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May 9, 2006

VIA HAND DELIVERY

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

Re: Comments Regarding Docket No. 2005P-0456

Dear Sir or Madam:

On behalf of a client, Rakoczy Molino Mazzochi Siwik LLP ("RMMS") submits the attached comments in support of the November 1, 2005 citizen petition filed by Sandoz Inc., regarding the determination of whether Wyeth discontinued its original formulation of Zosyn® (piperacillin and tazobactam for injection) for reasons unrelated to safety and efficacy. For the reasons set forth in RMMS' comments, the Agency should immediately grant Sandoz's petition.

As required by 21 C.F.R. § 10.30, we include an original and 4 copies of these comments.

Should you have any questions regarding these comments, please do not hesitate to contact us. RMMS appreciates the opportunity to provide these comments in support of the above-captioned petition, and requests that it be promptly granted so that all eligible ANDAs can be accepted and approved without delay.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

William A. Rakoczy

Christine J. Siwik

2005P-0456

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CJS/WAR/af
Enclosure

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May 9, 2006

VIA HAND DELIVERY

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

CITIZEN PETITION

Dear Sir or Madam:

On behalf of our client, Rakoczy Molino Mazzochi Siwik LLP hereby submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. §§ 10.20, 10.30, 320.21, 320.23.

A. ACTION REQUESTED

Petitioner respectfully requests that the Office of Generic Drugs of the U.S. Food and Drug Administration ("FDA") make the determination that Wyeth Pharmaceuticals, Inc. discontinued its original formulation for Zosyn® (piperacillin and tazobactam) for reasons unrelated to safety and efficacy and to allow companies to file Abbreviated New Drug Applications ("ANDA") seeking approval to market the original Zosyn® formulation. Specifically, Petitioner requests that FDA:

1. find that Wyeth discontinued its original formulation for Zosyn® (piperacillin and tazobactam) for reasons unrelated to safety and efficacy; and

2. accept ANDAs for piperacillin and tazobactam for injection, 2.25 grams, 3.375 grams and 4.5 grams, without edetate sodium and citric acid.

Any other action by FDA would run contrary to the controlling statutory and regulatory scheme, as well as run afoul of Congress' express intent when enacting the Hatch-Waxman Amendments to the FFDCA.[1]

B. STATEMENT OF GROUNDS

I. Introduction.

In deciding this Petition, FDA need only consider one question: Did Wyeth discontinue its original Zosyn® formulation for safety or efficacy reasons? As detailed below, the answer unequivocally is "no." No evidence – none – even suggests that the discontinued Zosyn® formulation is either unsafe or ineffective. Indeed, Wyeth's opposition to the Sandoz Petition contains no such evidence, nor could it given that Wyeth continued to market the discontinued formulation of its Zosyn® product long after FDA approved the reformulated product. This ends the matter. FDA should accept and approve ANDAs seeking to market the original Zosyn® formulation.

Wyeth's opposition contains no legal or scientific reason for FDA to deny this Petition, or the Sandoz Petition. Wyeth's opposition merely is yet another example of the anti-competitive tactics that brand companies have employed with more and more frequency.

FDA approved Wyeth's original Zosyn® formulation in October 1993. More than a decade later, the Agency approved Wyeth's new Zosyn® formulation on September 30, 2005. That formulation contains edetate disodium ("EDTA") and citric acid. While Wyeth's opposition to the Sandoz Petition puts forth an interesting story regarding the purported reasons behind the formulation change, the more plausible (and likely) explanation involves Wyeth's unending efforts to use its extensive patent portfolio to delay, if not prevent, generic competition. Specifically, Wyeth's opposition conveniently fails to mention that a patent covering its original Zosyn® formulation (U.S. Patent No. 4,933,444) will expire in February 2007, thus allowing manufacturers to bring generic Zosyn® products to market without litigation delays. Wyeth's reformulated Zosyn® product, too, purportedly is patent protected, but that protection extends for several more years. Consequently, if Wyeth's opposition prevails and ANDA applicants must use the new Zosyn® formulation, Wyeth could attempt to use its patent portfolio to prevent

[1] On November 1, 2005, Sandoz Inc. filed a citizen petition raising similar issues. FDA assigned that petition number 2005P-0456 (hereinafter, "the Sandoz Petition"). On January 20, 2006, Wyeth, in an attempt to delay generic competition, submitted comments opposing the Sandoz Petition. Sandoz responded to Wyeth's comments in a supplement dated March 1, 2006. This Petition references and discusses the Sandoz Petition, as well as Wyeth's comments in opposition thereto.

the introduction of lower-priced generic products for many years to come. Such a result would run contrary to the controlling statutory and regulatory scheme and, in the process, unnecessarily deny the public access to an affordable and safe generic Zosyn® product.

Recognizing the weakness of its position with respect to an ANDA applicant's right to obtain approval to market a discontinued formulation, Wyeth asks FDA to impose additional requirements on ANDA applicants seeking to market the discontinued Zosyn® formulation. As discussed more fully below, Wyeth's request has nothing to do with safety or efficacy, but, instead, is another part of its improper attempt to delay the generic market entry. FDA should reject Wyeth's request.

In sum, Wyeth did not voluntarily discontinue its original formulation of Zosyn® for reasons of safety or efficacy, as evidenced by its continued sales of that formulation. As such, FDA should accept and approve ANDAs seeking to market a generic version of Wyeth's original Zosyn® product. Denying this Petition would not only run afoul of controlling legal authorities, but also would serve to reward Wyeth's anti-competitive conduct and delay the public's access to a safe, efficacious, and lower-priced alternative to Wyeth's Zosyn® product.

II. Not Even Wyeth Disputes That It Discontinued The Original Zosyn® Formulation For Reasons Unrelated To Safety Or Efficacy.

The only relevant inquiry to this Petition is whether Wyeth discontinued its original Zosyn® formulation for safety and efficacy reasons. Without doubt, Wyeth voluntarily discontinued its original Zosyn® formulation for competitive business reasons, not safety or efficacy reasons. As such, FDA should grant this Petition.

The safety and efficacy of Wyeth's original Zosyn® formulation is evidenced by many undisputed facts. FDA, for example, determined this formulation to be safe and efficacious when it approved Wyeth's original NDA. Wyeth sold its original Zosyn® formulation for nearly thirteen years. Wyeth continued to sell its original Zosyn® formulation long after FDA approved the reformulated product and, in fact, apparently sold both the original and the new Zosyn® formulations at the same time. (*See* Wyeth Opposition at 14; http://www.wyeth.com/products/wpp_products/zosyn.asp (printed 3/27/06), Ex. A hereto). Wyeth has confirmed that the new formulation has not altered the dosing, safety profile or efficacy of Zosyn®. (*See* Sandoz Supp. Petition at Attachment 1 (Wyeth December 1, 2005 Dear Health Care Provider Letter)). FDA has never issued any notices of safety risks or recalls. And, of course, FDA did not ask Wyeth to reformulate Zosyn® – Wyeth did so as it saw patent protection for its original formulation coming to an end. Thus, all of the objective facts confirm that the discontinued Zosyn® formulation is safe and effective. Indeed, Wyeth's own actions and words confirm the safety and efficacy of its original Zosyn® formulation.

Because Wyeth did not discontinue its original Zosyn® formulation for reasons of safety and efficacy, ANDA applicants can obtain Agency approval to market that formulation. Accordingly, FDA should grant this Petition.

III. FDA Has The Authority To Accept And Approve ANDAs Seeking To Market A Formulation That The NDA-Holder Has Discontinued For Reasons Unrelated To Safety and Efficacy.

Wyeth's opposition to the Sandoz Petition challenges an ANDA applicant's right to market a formulation that the NDA-holder has discontinued for reasons unrelated to safety and efficacy. While the undersigned need not rebut Wyeth's arguments in order for FDA to grant this Petition, Wyeth's opposition necessarily fails. As discussed below, ANDA applicants can (and do) obtain FDA approval to market a safe and effective, but discontinued, formulation.

A. FDA Has The Authority To Accept And Approve ANDAs Seeking To Market The Original Zosyn® Formulation.

Wyeth's opposition to the Sandoz Petition goes on at length regarding the issue of whether an ANDA applicant can lawfully "reference" a product in the discontinued section of the Orange Book. (Wyeth Opposition at 6-7). In arguing that an ANDA applicant cannot lawfully use a discontinued formulation as a reference listed drug ("RLD"), Wyeth addresses a wholly irrelevant issue. Petitioner does not seek to file an ANDA using the discontinued Zosyn® formulation as the RLD. Petitioner's ANDA references the Zosyn® product currently in the Orange Book and seeks approval for the discontinued formulation, pursuant to FDA's waiver regulations.[2] This is entirely proper and lawful under FDA's regulations, which permit the Agency to approve a generic version of a formulation that the NDA-holder voluntarily discontinued for reasons unrelated safety or effectiveness. (*See* 21 C.F.R. § 314.122 and § 314.161). This also is fully consistent with prior Agency practice.

FDA previously has considered the impact of innovator formulation changes on ANDA applications and recognized that an applicant can submit, and the Agency can approve, an ANDA seeking approval to market a discontinued formulation. Specifically, under prior agency practice, an applicant seeking to submit an ANDA for a discontinued formulation need only do the following: reference the product currently in the active section of the Orange Book; certify to any Orange Book listed patents for the currently-marketed product; obtain an Agency determination that the NDA-holder discontinued the formulation for reasons other than safety and efficacy; and include a waiver request under 21 C.F.R. § 314.99(b). Once the Agency

[2] For this reason, Wyeth's citation of FDA's decision with respect to Cytoxan is inapposite. (Wyeth Opposition at 6-7). FDA did not rule that ANDA applicants were precluded from seeking approval to market the discontinued Cytoxan formulation, but merely that "any unapproved ANDAs seeking to reference Cytoxan (NDA 12-142 054) must reference the currently approved formulation." 69 Fed. Reg. 9630, 9631 (Mar. 1, 2004). Petitioner here does, in fact, reference the currently approved Zosyn® formulation in its ANDA, and does not seek to use the discontinued formulation as its RLD. Thus, the Cytoxan decision has no relevance to the situation at hand.

receives such an application and concludes that the brand company did not discontinue the formulation for safety or efficacy reasons, the ANDA can be approved where, as here, no listed patents or exclusivities prevent immediate approval. This is, in fact, precisely what the Agency has done with respect to other products. Take, for example, the situation surrounding Baxter's Brevibloc® (esmolol) 10 mg/mL.

FDA approved Baxter's Brevibloc® NDA in 1986. In 2003, FDA approved a new formulation for the product and moved Baxter's original 10 mg/mL Brevibloc® product to the discontinued section of the Orange Book. In August 2004, FDA determined that Baxter had discontinued its original 10 mg/mL Brevibloc® product for reasons unrelated to safety and efficacy. *See* 69 Fed. Reg. 47,155, 47,156 (Aug. 4, 2004). FDA concluded:

> Approved ANDAs that refer to the [Brevibloc® 10 mg/mL NDA] listed in this document are unaffected by the withdrawal of the product[] subject to [that NDA]. Additional ANDAs for the product[] may also be approved by the agency.

Id. After issuing its *Federal Register* notice, FDA went on to accept and approve several ANDAs for the withdrawn formulation of Baxter's 10 mg/mL Brevibloc® product.[3]

Similarly, with respect to the drug Sandostatin, FDA also permitted companies to submit ANDAs for the discontinued formulation where the Agency determined that the brand company had voluntarily discontinued the earlier formulation for reasons unrelated to safety or effectiveness. (*See* FDA 3/25/05 Admin. Ruling in 2001P-9574/CP1 and 2005P-0061/CP1 ("FDA Sandostatin Ruling"), Ex. B hereto). Specifically, FDA approved Sandostatin in 1988. (*Id.* at 2). In 1994, FDA approved a reformulated Sandostatin product in multidose vials, and, in 1995, approved that reformulation in ampules. (*Id.*). Years later, in 2002, Ben Venue sought a determination that NDA-holder Novartis discontinued the original Sandostatin product for reasons unrelated to safety and efficacy. (*Id.* at 1-2).[4] Sun Pharmaceuticals filed its own request seeking this same relief in 2005. (*Id.* at 1 n.1).

Novartis, like Wyeth here, opposed the Sandostatin petitions, arguing that "FDA regulations bar the approval of an ANDA for a proposed generic drug using the discontinued formulation of Sandostatin." (*Id.* at 2). FDA, of course, rejected that position. In granting Ben Venue's and Sun's petitions, FDA concluded that Novartis had discontinued its original Sandostatin formulation for reasons unrelated to safety or efficacy. (*Id.* at 9).

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[3] *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ESMOLOL%20HYDROCHLORIDE for listing of accepted and approved ANDAs. This list does not include the ANDAs seeking to market the discontinued Brevibloc® formulation that FDA has accepted, but not yet approved.

[4] As originally filed in 2001, Ben Venue's petition sought permission to refer to discontinued labeling for Sandostatin. (*Id.* at 1). In 2002, Ben Venue withdrew that request and sought a determination that Novartis discontinued the original Sandostatin product for reasons unrelated to safety and efficacy. (*Id.* at 1-2).

In sum, the situation here is not an issue of first impression, but rather one that FDA already, and repeatedly, has addressed – the brand company reformulated; it discontinued its original formulation for reasons unrelated to safety or efficacy; and ANDA applicants seek to market the original (now discontinued) formulation. The result here should be no different than in esmolol or Sandostatin, lest the Agency find itself in the untenable situation of treating similarly-situated parties differently. Once FDA finds that Wyeth discontinued its original Zosyn® formulation for reasons unrelated to safety and efficacy, it should allow companies to file applications seeking to market that formulation. This is the only result consistent with the controlling statute, FDA's regulations, and prior Agency determinations.

B. FDA Can Lawfully Waive Its Regulatory Requirement Relating To The Composition Of Parenteral Drug Products.

Wyeth also argues that FDA cannot approve an ANDA seeking to market the discontinued, original Zosyn® formulation. Wyeth is mistaken. FDA's regulations do not require an ANDA using a discontinued parenteral drug formulation to contain the same inactive ingredients as that of the current RLD so long as the inactive ingredients of the discontinued formulation are deemed to be safe and effective. More specifically, FDA has the discretion to waive the requirement that generic parenteral drugs contain the same inactive ingredients as the RLD. Thus, the absence of EDTA and citric acid in an ANDA product using the original formulation of Zosyn® does not serve as an obstacle to approval. An ANDA applicant can seek approval to market a generic version of the discontinued Zosyn® formulation that is therapeutically equivalent to the reformulated Zosyn® product. Indeed, FDA already has considered and rejected the arguments that Wyeth makes here when granting Ben Venue's and Sun Pharmaceutical's petition seeking to market a discontinued formulation of Novartis' Sandostatin product. (*See* FDA Sandostatin Ruling at 6-8).

In Sandostatin, the discontinued formulation used sodium chloride as the tonicity agent and a glacial acetic acid/sodium acetate buffer system, while the reformulation used mannitol as the tonicity agent and a lactic acid/sodium bicarbonate buffer system. Novartis, like Wyeth here, argued that FDA cannot approve an ANDA that contains inactive ingredients different from those used in the RLD. (*See id.* at 6-7). FDA flatly rejected this argument.

In rejecting Novartis' argument, the Agency first looked to the FFDCA, which provides in pertinent part:

> (H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive

> ingredients included or the manner in which the inactive ingredients are included; . . . .

21 U.S.C. § 355(j)(4)(H) (quoted and discussed in FDA Sandostatin Ruling at 6). And after determining that the inactive ingredients used in the discontinued Sandostatin formulation did not make the formulation unsafe, FDA concluded that "under the statutory standard, FDA would be justified in approving an ANDA that uses the discontinued formulation of Sandostatin." (FDA Sandostatin Ruling at 6).

FDA then turned to Novartis' argument that the Agency's regulations prevent approval of an original formulation once the brand reformulates to include different inactive ingredients, other than the different inactive ingredients listed in the regulations (*i.e.*, preservatives, buffers, and antioxidants).[5] The Agency, of course, correctly rejected that argument as well. FDA explained:

> Because an ANDA for the safe discontinued formulation of Sandostatin would clearly meet the statutory standard for approval under section 505(j)(4)(H) of the [FFDCA] Act, the Agency may rely on 21 CFR 314.99(b) to grant a waiver of the requirement that the ANDA and the NDA formulations contain the same inactive ingredients and the same concentration as the reference listed drug, with limited exceptions for preservatives, buffers, and antioxidants. This waiver provision states that "[a]n applicant may ask FDA to waive under this section any requirement that applies to the

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[5] FDA's ANDA content and format regulation provides:

> (iii) Inactive ingredient changes permitted in drug products intended for parenteral use. Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

21 C.F.R. § 314.94(a)(9)(iii). Similarly, the Agency's ANDA refusal to approve regulation provides:

> FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

21 C.F.R § 314.127(a)(8)(ii)(B).

> applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90."

(FDA Sandostatin Ruling at 8). FDA then explained that under 21 C.F.R. § 314.90, the Agency may grant a waiver if it finds that "(1) compliance with a regulatory requirement is unnecessary to evaluate the application, (2) the alternative submission satisfies the purpose of the requirement, or (3) the applicant's submission otherwise justifies the waiver." (*Id.*; *see also* 21 C.F.R § 314.90 and 21 C.F.R § 314.99(b)). From there, FDA concluded that granting a waiver to market the discontinued formulation would not involve any waiver of statutory requirements regarding inactive ingredients and thus was entirely lawful. (FDA Sandostatin Ruling at 8). As the Agency noted, "[t]his approach is a reasonable reading of FDA regulations, is justified by the science, and is consistent with the statutory requirements for ANDA approval." (*Id.*).

Applying the same regulations and statutory requirements to this Petition, Wyeth cannot prevail when arguing that FDA's regulations prevent the Agency from approving generic Zosyn® products that lack the EDTA found in Wyeth's reformulation because this ingredient is not a preservative, buffer, or antioxidant. (Wyeth Opposition at 8-9). Wyeth also cannot render the waiver provision inapplicable in this case with its half-hearted attempt to concoct some type of safety argument. (*Id.* at 9). Indeed, Wyeth fares no better than Novartis did when Novartis tried to manufacture a safety concern in the Sandostatin proceeding. (*See* FDA Sandostatin Ruling at 2-6).

Wyeth argues that FDA should not accept ANDAs for the original formulation because of the potential confusion that may occur among practitioners who choose the proposed generic product over the reformulated Zosyn®. Specifically, Wyeth states that because the original formulation, unlike the new formulation, is not compatible with certain aminoglycosides and the Lactated Ringer's Solution, the use of the proposed generic product would pose a potential health risk if practitioners are unaware of the differences between the two formulations. (Wyeth Opposition at 9). Wyeth's arguments lack merit. First, the fact that the original formulation cannot be used with either certain aminoglycosides or the Lactated Ringer's Solution in no way suggests that the formulation itself is unsafe. In fact, the original (now discontinued) formulation, when administered according to its approved labeling, is entirely safe. Wyeth provides no evidence to the contrary. Indeed, Wyeth sold this product for nearly thirteen years, and only reformulated that product for strategic commercial reasons. Second, the labeling for a proposed ANDA product will address any concerns that the original formulation could be administered incorrectly. For example, Wyeth's physician insert for its original Zosyn® product provides a list of all compatible reconstitution and intravenous diluents. (*See* Sandoz Petition, Ex. A at 20-21). The physician insert also warns against the use of Lactated Ringer's Solution and aminoglycosides with the original formulation. (*Id.* at 12 and 21). Sandoz's proposed physician insert contains identical language, as will the physician insert for any other ANDA seeking to market the original formulation. (*See* Sandoz Petition, Ex. C at 13, 22-23). Thus, the labeling of the proposed generic product will provide more than adequate protection against the

risk of improper administration of the drug. Accordingly, Wyeth provides the Agency with no reason to refrain from granting a waiver and allowing ANDA applicants to market the discontinued Zosyn® formulation.

Finally, Wyeth argues that an ANDA seeking to market the original Zosyn® formulation cannot meet FDA's bioequivalence and therapeutic equivalence requirements. (Wyeth Opposition at 10-11). FDA already dispensed with this argument in Sandostatin. In that ruling, FDA concluded that the original and reformulated products would, in fact, meet FDA's requirements:

> As stated in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." ***FDA's scientific expertise and experience have shown that such a difference in inactive ingredients would not preclude a finding of therapeutic equivalence.***

(FDA Sandostatin Ruling at 9 (footnote omitted and emphasis added)).[6]

Accordingly, FDA undoubtedly has the authority to accept ANDAs seeking to market the original Zosyn® formulation. This result is consistent with the FFDCA, FDA's regulations, and FDA's prior administrative rulings. As a result, FDA should grant the relief sought in this petition.

IV. FDA Should Reject Wyeth's Attempt To Impose Additional Regulatory Requirements On ANDA Applicants Marketing Generic Versions Of The Original Zosyn® Formulation.

Knowing that it cannot stop FDA from accepting and approving generic versions of the original Zosyn® formulation, Wyeth asks FDA to erect additional regulatory approval barriers to such products. Specifically, Wyeth asks FDA to require applicants to: (1) conduct

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[6] A finding of therapeutic equivalence requires a finding of bioequivalence. (*See* FDA's Orange Book, Introduction ("FDA classifies as *therapeutically equivalent those products that meet the following general criteria*: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) *they are bioequivalent* in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations." (Emphasis added)).

additional testing on the particulate matter of the proposed generic product; and (2) implement a risk minimization action plan ("RiskMAP"). (*See* Wyeth Opposition at 11-16). As an initial matter, these issues have nothing whatsoever to do with whether FDA can accept for filing ANDAs seeking approval to market the original Zosyn® formulation. More importantly, FDA should not impose these unnecessary approval requirements on ANDA applicants marketing generic versions of the original Zosyn® formulation.

First, FDA should not require ANDA applicants to conduct the additional and unnecessary testing on particulate matter that Wyeth demands. Wyeth states that it reformulated Zosyn® to address a problem with excess particulate matter in certain batches and that it tested the new formulation to ensure compliance with USP <788> on particulate matter. (Wyeth Opposition at 11). FDA, however, did not require Wyeth to reformulate its product, nor did it require Wyeth to perform testing on the particulate matter of its reformulated product. Yet, Wyeth insists that it is necessary to require applicants to conduct "[p]articulate matter testing under all possible conditions permitted in the product labeling, taking into account the many variables existing in clinical practice." (*Id.*). Wyeth fails to provide any reason why existing requirements for ANDA applicants are not sufficient to ensure compliance with applicable regulatory and USP standards. As such, applicants should not be forced to dedicate time and resources for any unnecessary testing.

Second, FDA should not require ANDA applicants to implement a RiskMAP. As discussed above, the proposed labeling of any ANDA seeking to market a generic Zosyn® product will provide adequate protection against any potential risks related to the administration of the drug product. Thus, any additional risk minimization measures, such as a RiskMAP, are unnecessary.

As FDA itself acknowledges, "[o]nly a few products are likely to merit consideration for additional risk minimization efforts." (*Guidance for Industry: Development and Use of Risk Minimization Action Plans*, at 4 (Mar. 2005)). Indeed, as FDA has explained, RiskMAPs are by far the exception and not the rule:

> [F]or most products, routine risk minimization measures are sufficient. Such measures involve, for example, FDA-approved professional labeling describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from postmarketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. *Efforts to make FDA-approved professional labeling clearer, more concise, and better focused on information of clinical relevance reflect the Agency's belief that communications of risks and benefits through product labeling is the cornerstone of risk management efforts for prescription drugs.*

> *For most products, routine risk management will be sufficient and a RiskMAP need not be considered.*

(*Id.* at 4-5 (emphasis added and footnote omitted)).

Here, the proposed labeling for generic Zosyn® products will adequately address any concerns regarding the administration of the drug. A RiskMAP is unnecessary because it will do little to further improve the safety of a generic Zosyn® product.

Moreover, FDA did not require Wyeth to implement a RiskMAP when approving Wyeth's sNDA for the reformulated Zosyn®. Any effort by Wyeth to educate its customers and sales force on the differences on the two Zosyn® products was self-serving, no doubt rooted in a desire to encourage its existing customers to switch from the original Zosyn® to the reformulated Zosyn®. If FDA believed that having both Zosyn® products on the market created a safety problem that could not be addressed by existing safeguards, it plainly would have required Wyeth to implement a RiskMAP. Wyeth does not allege that the Agency has required such action.

Finally, even if FDA were inclined to consider these issues (it should not be), such issues are for another time. Petitioner seeks a determination that Wyeth did not discontinue its original Zosyn® formulation for safety or efficacy reasons and to have its ANDA accepted for filing. Particulate matter testing and RiskMAPs have nothing to do with the relief Petitioner seeks. Thus, while FDA should reject Wyeth's requests for the reasons set forth above, under no circumstances should FDA decline to grant the relief requested herein because of Wyeth's requests on these issues.

V. Conclusion.

FDA already made the determination that the discontinued formulation of Zosyn® is safe when it granted Wyeth's NDA to market and sale the drug. Further, there is no evidence that Wyeth chose to withdraw the original formulation for reasons of safety or efficacy. Moreover, in its opposition to the Sandoz Petition, Wyeth fails to even assert that the discontinued formulation is unsafe. Accordingly, we respectfully request that FDA find that the discontinued Zosyn® formulation was not withdrawn for reasons of safety or efficacy, and accept the submission of ANDAs that use the formulation.

C. ENVIRONMENTAL IMPACT

Under 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition that are unfavorable to the petition.

Respectfully submitted,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

William A. Rakoczy

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