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Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket 2005P-0456/CP1

Dear Sir or Madam:

Wyeth Pharmaceuticals ("Wyeth") submits these comments in response to the November 1, 2005 citizen petition filed by Sandoz Inc. ("Sandoz"). The petition requests that the Food and Drug Administration ("FDA") determine that a discontinued formulation of Zosyn® (piperacillin and tazobactam for injection) was not discontinued for reasons of safety or effectiveness. In addition, the petition requests FDA to accept Sandoz's abbreviated new drug applications for formulations duplicating the discontinued Zosyn® formulation.

As discussed in these comments, the petition's request that FDA accept abbreviated new drug applications for products referencing the discontinued Zosyn® formulation should be denied for two reasons:

- (1) Proposed generic products are not legally permitted to use discontinued formulations of existing products as reference drugs.
- (2) Approving a generic version of Zosyn® that lacks the inactive ingredients in the current formulation of Zosyn® would be contrary to FDA regulations and the public health.

If, notwithstanding these substantial legal and regulatory concerns, FDA is nevertheless prepared to accept applications for Sandoz's proposed products, any approval should be contingent upon two factors:

- (1) The generic products should be required to comply with the U.S. Pharmacopoeia standard on particulate matter in a wide range of actual use conditions, as Zosyn® does.

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- (2) The generic applicant should be required to implement an effective risk minimization action plan. Generic products based on the discontinued Zosyn® formulation would have significant differences in their acceptable conditions of use compared to the reformulated version of Zosyn®. It is essential that healthcare practitioners be continually made aware of those differences to prevent errors affecting the safe use of the generic versions.

I. BACKGROUND

A. Zosyn® Products

Zosyn® (piperacillin and tazobactam for injection) is a combination antibacterial product used for treating certain infections. Wyeth distributes the product in several presentations: (1) standard vials, (2) ADD-Vantage® vials, (3) pharmacy bulk vials, and (4) Galaxy® containers. When distributed in vials, Zosyn® is in the form of a powder; when in Galaxy® containers, it is in the form of a frozen solution. According to its petition, Sandoz is seeking approval of generic versions of Zosyn® packaged in standard and ADD-Vantage® vials.

To use a powdered version of Zosyn®, the product is first reconstituted in the vial using a compatible diluent, as identified in the package insert. The reconstituted Zosyn® solution is then further diluted in a compatible intravenous solution, as identified in the package insert, by transferring the product to an infusion bag. After reconstitution in the vial and dilution in the infusion bag, Zosyn® is administered to patients by intravenous infusion.

B. Particulate Matter in Injectable Products

Injectable products inevitably contain very small amounts of subvisible particulate matter. If particulate matter is present in excess quantity, it can cause adverse health effects.¹ Clinical evidence indicates that intravenous treatments with lower levels of particulate contamination are associated with a reduction in the incidence of adverse events.² As a result, manufacturing specifications limit the amount of acceptable particulate matter, and the U.S. Pharmacopoeia (“USP”)

¹ See Nrapendra Nath et al., *Particulate Contaminants of Intravenous Medication and the Limits set by USP General Chapter <788>*, 30 *Pharmacopeial Forum* 2272 (2004).

² KH Falchuck, et al., *Microparticulate-induced phlebitis. Its prevention by in-line filtration*, 312 *New Eng. J. Med.* 78 (1985); Hans-anton Lehr, et al., *Particulate Matter Contamination of Intravenous Antibiotics Aggravates Loss of Functional Capillary Density in Postischemic Striated Muscle*, 165 *Am. J. Respiratory and Critical Care Med.* 514 (2002); R. Leon Longe, *Particulate Contamination in Selected Parenteral Drugs*, 27 *Can. Anesthesia Soc’y J.* 62 (1980).

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has established a standard on particulate matter in injectable drugs (“Particulate Matter in Injections”) in General Chapter <788>.³

Particulate matter is often the result of the manufacturing process used. As is discussed below, however, particulate matter in injectable products can also result from chemical interaction between reconstituted product and the infusion bags and other material used for administering the product.

When the new drug application (“NDA”) for Zosyn® was approved in 1993, the USP <788> limits on particulates were no more than 10,000 for particles $\geq 10\mu\text{m}$ and no more than 1,000 for particles $\geq 25\mu\text{m}$. These specifications and acceptance criteria were included in the approved NDA for Zosyn® in 1993. In 1995, USP updated <788> to lower the limits to no more than 6,000 for particles $\geq 10\mu\text{m}$ and no more than 600 for particles $\geq 25\mu\text{m}$. Similar particulate limits have been instituted in both Europe and Japan.⁴

C. Particulate Matter in Zosyn®

In 2000 and 2001, Wyeth discovered unexpected levels of subvisible particulate matter in certain batches of Zosyn®, and FDA indicated that the levels should be reduced. Wyeth immediately began investigations to control particulate levels in the product. Wyeth also committed to FDA that it would study the nature and cause of the particulate formation in order to resolve the issue.

Wyeth then began a period of systematic testing and analysis in order to determine the mechanism of particulate formation in Zosyn®. Wyeth concluded that the particulates generally consisted of either piperacillin monohydrate (“PMH”) or silicone. The PMH particulates resulted from a conversion of the drug’s piperacillin active ingredient into PMH by chemical reaction or by precipitation in solutions with low pH. The silicone particles were eliminated by incorporating new manufacturing processes that rendered a silicone oil lubricant unnecessary.

The nature and level of the particulates did not present a clinically significant safety concern. Steps taken by Wyeth, however, eliminated the excess particulate matter to FDA’s satisfaction.

³ USP <788> “Particulate Matter for Injections.”

⁴ European Pharmacopoeia, General Notices § 2.9.19 “*Particulate contamination: sub-visible particles*”; Japanese Pharmacopoeia, General Rules for Preparations § 11 (13) “*Injections*.”



D. Particulate Matter in Protonix® IV

In that same time period, Wyeth was developing Protonix® IV (pantoprazole sodium) for Injection (“Protonix® IV”), a proton pump inhibitor indicated for treatment of gastroesophageal reflux disease. During the approval process, FDA expressed concerns to Wyeth about the level of particulate matter in the product.

FDA’s concern led to a requirement that an in-line filter be packaged with each vial of the product until it could be reformulated to reduce particulate counts to acceptable levels. Wyeth agreed to post-marketing commitments including: (1) identification of the conditions and substances promoting precipitation of particulate matter in the product, (2) evaluation of commonly used diluents and their effects on particulate levels in the product, and (3) reformulation of the product to reduce particulate levels.

During the Protonix® IV approval process and afterwards, Wyeth analyzed the cause of the particulates in Protonix® IV. The analysis determined that the particles were generally caused by: (1) precipitation in solutions with low pH or (2) chemical reactions that were catalyzed by metal ions. Wyeth found that low pH of Protonix® IV solutions could result from the use of acidic admixture diluents or from acidic degradation products. Wyeth also learned that metal ions could come from a variety of sources such as metallic manufacturing surfaces, admixture solutions, vial stoppers, septa, and IV-bag tubing. The most significant variable was found to be the intravenous solution used to administer the drug, as these solutions vary widely in their concentration of metal ions and their pH.

With this information, Wyeth reformulated Protonix® IV to eliminate the excess particulates. Sodium hydroxide as a buffer and edetate disodium as a chelating agent were added to the formulation, and these changes reduced particulate matter to acceptable levels. FDA approved the new formulation of Protonix® IV and eliminated the requirement that the product be packaged with an in-line filter.

E. Reformulation of Zosyn®

Because Zosyn® and Protonix® IV had similar particulate issues, Wyeth expected that FDA would, at some point, require it to reformulate Zosyn® just as FDA had required the reformulation of Protonix® IV, even though the initial particulate issue with Zosyn®, discussed above, had been resolved. In addition, in 2001 USP began developing a monograph for piperacillin and tazobactam for injection. The monograph would incorporate the 1995 USP <788> specifications, which were tighter than the specifications included in Zosyn’s NDA. After

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Protonix® IV had been reformulated, Wyeth turned its attention to reformulating Zosyn® so that it would comply with USP <788>.

As previously mentioned, Wyeth had expanded its knowledge during its Protonix® IV research, learning that levels of particulate matter were associated with pH levels and levels of metal-ion concentration. Particulate levels were found to be highest when the reconstituting solution had either (1) a low pH level or (2) a high level of metal ions. A new formulation of Zosyn® (“Reformulated Zosyn”) was created to resist particulate formation caused by these factors. Reformulated Zosyn contains citric acid monohydrate, which acts as a buffer to control pH, and edetate disodium dihydrate (“EDTA”), which acts as a chelating agent.⁵ Due to the addition of these ingredients, Reformulated Zosyn can tolerate all extremes of metal ion and pH found in various reconstituting solutions. Reformulated Zosyn also complies with the 1995 USP <788> particulate matter specifications, demonstrating significantly lower levels of particulate formation than the first Zosyn® formulation (“Original Zosyn”). FDA approved Reformulated Zosyn on September 30, 2005.

In addition to being a more robust product, Wyeth found that Reformulated Zosyn was compatible with certain substances with which Original Zosyn is not compatible. One such substance is Lactated Ringer’s Solution, which is commonly used as an intravenous solution for reconstitution. It is also used for fluid resuscitation after blood loss in trauma patients, in which case reconstituted Reformulated Zosyn may be co-administered. Because the approved product labeling for Original Zosyn informed users that Original Zosyn may not be reconstituted with Lactated Ringer’s Solution, the labeling for Reformulated Zosyn was revised to indicate this new compatibility.

In addition, Reformulated Zosyn is also compatible with two commonly used aminoglycoside antibiotics, amikacin and gentamicin. Original Zosyn is not compatible with any aminoglycoside antibiotics and the product labeling instructs the user to exercise care to administer such products separately. *In vitro* mixing of Original Zosyn and the aminoglycoside class of antibiotics can result in inactivation of the aminoglycoside. This fact is noteworthy particularly in the context of diseases such as nosocomial pneumonia, for which the concomitant administration of Zosyn® and an aminoglycoside antibiotic is indicated.⁶ Reformulated Zosyn, however, may be co-administered with amikacin and

⁵ In the case of Zosyn® in Galaxy® containers, only EDTA was added in the new formulation. The original formulation already contained citric acid monohydrate.

⁶ Zosyn® Prescribing Information (for both Original Zosyn and Reformulated Zosyn).

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gentamicin via a Y-site or multiple-port infusion system. The labeling for Reformulated Zosyn reflects this new compatibility.

II. ANDAS MAY NOT REFERENCE DISCONTINUED FORMULATIONS OF LISTED DRUGS

Contrary to the request in its petition, Sandoz may not legally use Original Zosyn (i.e., the discontinued formulation of Zosyn®) as the reference listed drug for its abbreviated new drug applications (“ANDAs”). The FDA regulation on which Sandoz attempts to rely, 21 C.F.R. § 314.122, does not support its petition.

That regulation permits an ANDA to rely on “a listed drug that has been voluntarily withdrawn from sale,” so long as FDA determines that the withdrawal was not for safety or effectiveness reasons.⁷ Sandoz’s petition seeks an FDA determination that a discontinued formulation of a marketed drug can be considered a “listed drug,” but Sandoz’s interpretation is not supported by FDA’s rules.

A “listed drug” is “evidenced by [its] identification as a drug with an effective approval in the current edition of FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations*” (the “Orange Book”).⁸ The determination of whether a given drug is a “listed drug” is thus directly related to the listings in the Orange Book. The Orange Book listing of a given drug does not, however, change each time that drug is reformulated, and different formulations of the same drug are not listed. Therefore, under 21 C.F.R. § 314.3, a “listed drug” must be interpreted to mean the current formulation of a drug and not a superseded formulation.

As recently as 2004, FDA made clear that ANDAs may not be based on discontinued formulations when it denied a petition similar to Sandoz’s.⁹ After receiving approval for an initial formulation of Cytoxan (cyclophosphamide for injection) (“Original Cytoxan”), Bristol Myers Squibb (“Bristol”) received approval for a new, lyophilized formulation and withdrew Original Cytoxan from the market. ASTA Medica, Inc. subsequently submitted a citizen petition requesting that FDA determine whether Original Cytoxan was withdrawn for reasons of safety or efficacy, just as Sandoz has done in the current proceeding.

⁷ 21 U.S.C. § 355(j)(7)(C); 21 C.F.R. § 314.122(c).

⁸ 21 C.F.R. § 314.3.

⁹ Determination That Cytoxan (Cyclophosphamide for Injection), 2 Gram Vials (NDA 12-142 054), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 69 Fed. Reg. 9630 (Mar. 1, 2004).

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In a notice dated March 1, 2004, FDA refused to allow ASTA Medica, Inc. to reference Original Cytoxan in its ANDA, despite finding that Bristol had not withdrawn Original Cytoxan from sale for reasons of safety or efficacy. FDA stated:

Because Bristol has supplemented its Cytoxan NDA and obtained approval for a new formulation . . . any unapproved ANDAs seeking to reference Cytoxan as a reference listed drug must reference the currently approved formulation.¹⁰

The same reasoning should apply in this case. Because Wyeth supplemented its Zosyn® NDA and obtained approval for a new formulation (Reformulated Zosyn), ANDAs seeking to reference Zosyn®, such as Sandoz's ANDA, must reference the currently approved formulation.

Interpreting 21 C.F.R. § 314.122 to permit ANDAs to reference previous formulations of a currently marketed drug would be incompatible with FDA's desire to "avoid possible significant variations among generic drugs and their brand-name counterpart."¹¹ The "significant variations" that FDA wishes to avoid would be a highly probable outcome if discontinued formulations of drugs were permitted as reference drugs for ANDAs. Consider, for example, a situation in which a drug is reformulated multiple times. Even if the differences between each successive formulation are not significant, the differences between the original formulation and the newest formulation could be considerable. Under Sandoz's proposed interpretation of 21 C.F.R. § 314.122, an ANDA applicant could use the oldest formulation as a reference drug, even though the brand-name counterpart of the proposed drug would be the newest formulation. The likely consequence of such an interpretation would be the exact result that FDA seeks to avoid, namely "significant variations" among generics and their brand-name counterparts.

¹⁰ *Id.*

¹¹ Center for Drug Evaluation and Research, Food and Drug Administration, *Approved Drug Products with Therapeutic Equivalence Evaluations*, at xi (25th Ed. 2005), at <http://www.fda.gov/cder/orange/obannual.pdf>.

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III. PERMITTING A GENERIC VERSION OF ZOSYN® TO HAVE THE INGREDIENTS OF THE ORIGINAL FORMULATION WOULD BE CONTRARY TO FDA REGULATIONS AND THE PUBLIC HEALTH

A. ANDAs for Piperacillin and Tazobactam Products Must Include EDTA

The underlying purpose of the Sandoz petition is to permit its proposed products to omit the inactive ingredients citric acid monohydrate and EDTA that are used in Reformulated Zosyn. These proposed changes in the formulation, however, are not permitted by the FDA regulations.

Generally, a generic injectable drug must contain the same inactive ingredients as the reference drug.¹² Differences in preservatives, buffers, and antioxidants are permitted, but the applicant must demonstrate that such differences do not affect the safety or efficacy of the proposed drug.¹³ Other differences in chemical composition are not permitted.¹⁴

As stated above, citric acid monohydrate was incorporated in Reformulated Zosyn to control the pH of the reconstituted drug and thereby decrease the presence of particulate matter. Because citric acid monohydrate acts as a buffer, a generic product based on Zosyn® could, under the regulations, omit citric acid monohydrate or use a different buffer, provided that the resulting product was equally safe and effective and met all other requirements, including limitations on particulate matter.

EDTA, on the other hand, functions as a chelating agent in Reformulated Zosyn. The chelation control provided by EDTA prevents metal ions existing in intravenous solutions and packaging components, and resulting from manufacturing processes, from reacting with the product and forming particulate matter. Although it may be argued that EDTA is also commonly used as a preservative, in the context of an approval of a generic drug, the word “preservative” relates to “the *function* of the inactive ingredient in the formulation” (emphasis added).¹⁵ Because EDTA functions as a chelating agent and not as a preservative in Reformulated Zosyn, it should not be considered a preservative for purposes of an exception under 21 C.F.R. § 314.94(a)(9)(3).

¹² 21 C.F.R. § 314.94(a)(9)(3).

¹³ *Id.*

¹⁴ See 21 C.F.R. § 314.127(a)(8)(ii)(B).

¹⁵ *Zeneca, Inc. v. Shalala*, 1999 U.S. Dist. LEXIS 12327 (D. Md. Aug. 11, 1999), *aff'd* 213 F.3d 161 (4th Cir. 2000).

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Therefore, an ANDA for piperacillin and tazobactam injection can only be approved if it contains EDTA.

B. Generic Products With Inactive Ingredients Different From Reformulated Zosyn Would Create Public Health Risks

The perpetual risk of improper substitution of a generic product based on Original Zosyn for Reformulated Zosyn should necessitate the rejection of an ANDA for such a generic product. The relevant differences between uses of the two formulations can be summarized as follows:

- (1) Reformulated Zosyn may be combined *in vitro* with certain aminoglycosides whereas Original Zosyn may not; and
- (2) Reformulated Zosyn is compatible with Lactated Ringer's Solution whereas Original Zosyn is not.

Because generic products are usually required to have the same conditions of use as their brand-name counterparts¹⁶ and because Reformulated Zosyn and Original Zosyn differ significantly in some conditions of use, it is foreseeable that the differences between Reformulated Zosyn and a generic product based on Original Zosyn will cause confusion among practitioners. Furthermore, healthcare providers who administer drugs are often not the same individuals who decide whether a healthcare facility will use a brand-name drug or its generic counterpart. The separation of decision-makers from practitioners has the potential to cause confusion among practitioners as to whether they are using a brand name drug or a generic. In the case of Reformulated Zosyn and a generic product based on Original Zosyn, this confusion may result in substandard patient care.

Consider a physician who uses Reformulated Zosyn with Lactated Ringer's Solution. It is foreseeable that this physician or a pharmacist might (1) substitute the proposed generic product for Reformulated Zosyn and (2) assume, as is natural to do, that the generic product can be used in the same manner as Reformulated Zosyn. The physician would then continue to use Lactated Ringer's Solution for reconstitution, resulting in the inactivation of the active ingredient of the generic product and suboptimal patient care, at best. Rejecting ANDAs referencing Original Zosyn will prevent such results from occurring.

¹⁶ 21 C.F.R. § 314.92(a)(1).

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C. The Proposed Change in Inactive Ingredients Is Incompatible with FDA's Bioequivalence Waiver and Therapeutic Equivalence Requirements

Sandoz's proposed products can be approved only if they are shown to be bioequivalent to their reference listed drug, unless the requirement for bioequivalence is waived.¹⁷ An ANDA must contain either (1) evidence of bioequivalence or (2) information sufficient to conclude that the proposed product and the reference drug are bioequivalent, thereby permitting FDA to waive the submission of evidence of bioequivalence.¹⁸ In order for a sponsor of a parenteral product to obtain such a waiver, however, the bioequivalence of the proposed product to the referenced drug must be "self-evident," meaning that the proposed product must contain "the same active and inactive ingredients" as the referenced drug.¹⁹

If Sandoz's products do not contain EDTA, then the products would not contain the same inactive ingredients as Reformulated Zosyn. The bioequivalence of the proposed product and Reformulated Zosyn, therefore, would not be "self-evident." The sponsor of the proposed product would then be required, under 21 C.F.R. § 320.21(b), to submit evidence of the bioequivalence of its product and Reformulated Zosyn.

In addition, while the Orange Book provides that therapeutic equivalents are permitted to differ in "minor aspects of labeling," the differences between the labeling of a proposed generic product based on the formulation of Original Zosyn and the labeling of Reformulated Zosyn would be significant.²⁰ The generic product's label would have to notify users that the product is not compatible with Lactated Ringer's Solution and that the product cannot be combined with aminoglycoside antibiotics. Such considerable variations in labeling can hardly be considered "minor" and as such, the generic product could not be rated in the Orange Book as a therapeutic equivalent to Reformulated Zosyn.

In short, the products proposed by Sandoz would not be therapeutically equivalent to Zosyn®, and Sandoz would need to show bioequivalence in a manner not ordinarily required for parenteral drugs. The incompatibility of Sandoz's

¹⁷ 21 C.F.R. § 320.21(b).

¹⁸ *Id.*

¹⁹ 21 C.F.R. § 320.22(b)(1)(ii).

²⁰ *Approved Drug Products with Therapeutic Equivalence Evaluations*, *supra* n. 9, at viii.



proposed products with the general rules for generic drugs illuminates the problems with Sandoz's petition.

IV. ANY GENERIC PRODUCTS REFERENCING ZOSYN® SHOULD BE RIGOROUSLY TESTED TO ENSURE COMPLIANCE WITH THE USP SPECIFICATIONS ON PARTICULATE MATTER

As summarized above, several years ago FDA expressed concern regarding the particulate matter that formed in Original Zosyn under certain circumstances. At about the same time, FDA required Wyeth to reformulate its Protonix® IV product to reduce particulate formation that was caused by the similar mechanisms as the particulate formation in Zosyn®. Consequently, Wyeth also reformulated Zosyn® so that it would fully comply with the particulate limitations in USP <788>.

Any generic version of Zosyn® should be held to same standards as Zosyn® and should be required to comply with USP <788>. As indicated in the earlier discussion in these comments, formation of particulate matter is in part related to the presence of metal ions in the intravenous solutions, bags, and supplies used in administration of the product. Since these solutions and supplies differ greatly in their metal ion content and tendency to react with Zosyn®, Wyeth tested its reformulated product in a wide variety of circumstances to ensure that USP <788> would be met in foreseeable conditions of use.

Sponsors of generic products based on Zosyn® should therefore be required to conduct similar wide-ranging and robust testing and analysis, as was conducted by Wyeth. Particulate matter testing under all possible use conditions permitted in the product labeling, taking into account the many variables existing in clinical practice, would be necessary to demonstrate compliance with the USP <788>.

V. ANY APPROVAL OF A GENERIC PRODUCT BASED ON ORIGINAL ZOSYN SHOULD BE CONTINGENT ON THE SPONSOR'S ADOPTION OF AN EFFECTIVE RISK MINIMIZATION ACTION PLAN

As detailed in the preceding sections of these comments, any approval of an ANDA based on Original Zosyn would be inconsistent with FDA regulations and contrary to the public health. If FDA does approve such an ANDA, however, it should at least require the sponsors of such ANDAs to take aggressive steps to minimize the health risks that their products will create.

Any FDA approval of a generic product based on Zosyn® but lacking a suitable buffer and EDTA would increase the risk of improper administration of the

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generic product. The differences in conditions of use between the generic product and Reformulated Zosyn, such as compatibility with Lactated Ringer's solution and *in vitro* combination of the drug with certain aminoglycosides, will cause confusion among physicians and other healthcare professionals and will, in turn, lead to increased risks of improper administration and the potential reduction of efficacy of the products.

Healthcare professionals are accustomed to using generic products and their brand-name counterparts interchangeably; consequently, the differences between Reformulated Zosyn and a generic version based on Original Zosyn would give rise to risks of medical errors that cannot be addressed by routine risk management measures. Even if only one product (Reformulated Zosyn or the generic) will be available for use at any given healthcare facility, the fact that many healthcare providers have clinical privileges at multiple healthcare facilities highlights the need to provide continuous education and communication regarding the differences between the products. Any approval of an ANDA referencing Original Zosyn should therefore be conditioned upon the generic sponsor's adoption of a risk minimization action plan (a "RiskMAP").

A. RiskMAPs Generally

In March 2005, FDA released three final guidance documents, each focusing on a different aspect of risk management: assessment of pre-marketing risk, assessment of post-marketing risk, and risk minimization.²¹ The guidance documents define RiskMAPs as strategic programs "designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits."²² FDA discusses several types of RiskMAP tools, including (1) education and outreach tools and (2) reminder systems.

FDA recommends education and outreach tools when routine risk minimization is known or is likely to be insufficient in minimizing product risks. These tools employ specific and targeted efforts "to increase appropriate knowledge and behaviors of key people or groups (e.g., healthcare practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern."²³ In addition, these tools can be used to explain how drug products should be used in order to maximize benefits (e.g., educating physicians about the effects of

²¹ See FDA, *Guidance for Industry: Premarketing Risk Assessment* (Mar. 2005); FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (Mar. 2005); FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans* (Mar. 2005).

²² FDA, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, at 5.

²³ *Id.* at 8.

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changes in temperature on the potency of a drug) and minimize risks (e.g., educating consumers to take drug products according to labeled instructions). Examples of tools in this category include informational letters to healthcare practitioners and professional or public notifications.

FDA recommends tools in the reminder-system category when targeted education and outreach tools are insufficient to minimize identified risks. These types of tools can “prompt, remind, double-check, or otherwise guide healthcare practitioners in prescribing, dispensing, receiving, or using a product in ways that minimize risk.”²⁴ Tools in this category include training programs that test a healthcare provider’s knowledge and understanding, specialized packaging to enhance safe use of the product, and specialized records such as prescription stickers that are used to attest that safety measures have been satisfied.

B. Wyeth’s Risk Minimization Program

Wyeth anticipated that the introduction of Reformulated Zosyn and the removal of Original Zosyn from the market could give rise to confusion among practitioners during the transition period. Accordingly, Wyeth developed a comprehensive and detailed communication program to help practitioners differentiate between the two formulations during the estimated ten-week period in which both formulations will be concurrently available in the market. Designed to minimize medical error and protect patient safety, the program will be implemented in conjunction with the introduction of Reformulated Zosyn.

The communication program consists of many components and employs a multi-faceted approach. First, new materials were developed for Zosyn® sales representatives to help them understand the differences between Original Zosyn and Reformulated Zosyn and communicate those differences to practitioners. The materials include internal training resources, a flip-chart style visual aid, a compatibility flashcard, and an informational dosing card. These materials discuss the compatibility information for Reformulated Zosyn with amikacin and gentamicin in detail (Zosyn® dose amount and form, diluent volume, aminoglycoside concentration range, and acceptable diluents). They also note the new compatibility with Lactated Ringer’s Solution and point out the differences in packaging and NDC codes for Original Zosyn and Reformulated Zosyn. Four hundred sales representatives were trained and certified on these materials, as well as on the new label for Reformulated Zosyn.

²⁴ *Id.* at 9.

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Second, the packaging for Zosyn® was redesigned to include a yellow background so that healthcare providers can easily distinguish between Reformulated Zosyn and Original Zosyn packaging.

Finally, concurrently with the introduction of Reformulated Zosyn, Wyeth distributed a detailed letter announcing both the availability of the product and the expanded compatibility of the product. The letter was distributed through conventional direct-mail channels and via email to over 5,000 hospitals and more than 10,000 other recipients, including all Wyeth wholesalers and more than ninety percent of group purchasing organizations, long-term care facilities, managed care organizations, pharmacy benefit managers, and chain pharmacies. The letter, like the materials described above, both highlights the expanded compatibility of Reformulated Zosyn and reminds practitioners that Original Zosyn does not have this expanded compatibility.

Wyeth is thus employing a three-pronged approach in delivering its message about Reformulated Zosyn and its important differences from Original Zosyn: (1) a direct-mail and email campaign notifying practitioners of the message; (2) an experienced sales force equipped with the necessary tools to help deliver and reinforce the message; and (3) packaging has been altered so as to remind practitioners of the message at the time of use. This three-pronged approach helps ensure that healthcare providers remain aware of the differences between the two products, regardless of whether the different facilities to which they have clinical access use only one product or both products.

C. Proposed RiskMAP For a Generic Product Based on Zosyn®

As the time in which Original Zosyn and Reformulated Zosyn are concurrently available in the market is estimated to last only ten weeks, it is not necessary for Wyeth's communication program to address the long-term effects of having two different products on the market. The existence of a generic product based on Original Zosyn, however, would create additional and sustained confusion in the marketplace among practitioners, particularly if use of Reformulated Zosyn with certain aminoglycoside antibiotics and Lactated Ringer's Solution is established as a standard practice during the extended period of time in which only Reformulated Zosyn is available. Therefore, a RiskMAP implemented by the sponsor of such a generic product should incorporate the steps taken by Wyeth as well as additional steps to ensure that the risk of confusion and improper administration of the generic product is minimized.

A RiskMAP comprised of education, outreach, and reminder tools would minimize the risks associated with having Reformulated Zosyn and a generic

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product lacking a buffer and EDTA on the market at the same time “without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients.”²⁵ As such, it is essential that a generic sponsor establish a RiskMAP addressing the risks arising from the differences in the conditions of use of its product and Reformulated Zosyn. Because manufacturers of generic products typically do not interact with individual practitioners, it is all the more important that FDA require such a RiskMAP to include components directly communicating to this population. The RiskMAP should, throughout the life of the generic product, also include:

- distribution of information to healthcare practitioners, healthcare facilities, and those responsible for the bulk purchase of drug products communicating the differences between the generic product and Reformulated Zosyn;
- ongoing training programs for healthcare practitioners to raise awareness of the differences between the generic product and Reformulated Zosyn, with components designed to test the participant’s knowledge and understanding of the topics covered;
- press releases and periodic notifications in professional medical journals describing the differences between the generic product and Reformulated Zosyn; and
- specialized product packaging to encourage correct use of the generic product and discourage incorrect use.
- programs specifically addressing the risk of improper administration that is presented when a physician or a nurse practices in two or more healthcare facilities, where one facility uses Reformulated Zosyn and the other uses the generic product.

D. RiskMAP Evaluation

A RiskMAP implemented by a generic sponsor should be monitored and evaluated in order to identify areas for improvement. This kind of evaluation will help “ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks,” which FDA has stated is the objective of RiskMAPs.²⁶ A RiskMAP containing an

²⁵ *Id.* at 5.

²⁶ *Id.* at 13.

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evaluation component would be consistent with the FDA recommendation that “every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation.”²⁷

VI. CONCLUSION

Sandoz’s petition should be denied. Discontinued formulations of existing products are not legally available for use as reference drugs in ANDAs, as Sandoz requests. Moreover, by omitting important inactive ingredients in Reformulated Zosyn, Sandoz’s proposed products would not comply with FDA’s regulations and would be inconsistent with public health considerations.

If, despite these factors, FDA is nevertheless willing to approve an ANDA referencing Original Zosyn, FDA should ensure that the product meets the particulate matter specifications in USP <788>, as Zosyn® does, and should condition such approval upon the sponsor’s implementation of a comprehensive RiskMAP to minimize the risks associated with a generic drug that would significantly differ from Zosyn® in appropriate conditions of use.

Sincerely,



Geoffrey M. Levitt
Vice President & Chief Counsel
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cc: Janice Soreth, M.D. Director
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²⁷ *Id.*