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Safety and Legal Issues Raised by Generic Piperacillin/Tazobactam Products that Differ from the Reformulated Version of Zosyn®

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Wyeth
Pharmaceuticals

Wyeth Participants

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Overview of the Issues

- Wyeth reformulated Zosyn® to ensure compliance with revised USP particulate standards
 - ▶ The reformulated version of Zosyn® received approval in September 2005 and was launched in January 2006
- Unlike the original formulation, the reformulated version of Zosyn® is compatible with Lactated Ringer's Solution and certain aminoglycoside antibiotics
- Generic piperacillin/tazobactam products based on the original Zosyn® formulation raise significant safety and legal issues due to the differences between the original and the reformulated versions of Zosyn®

Overview of the Safety Issues

- **Safety Issues**

- ▶ Medication Errors
- ▶ Particulates

Overview of the Legal Issues

- **Legal Issues**

- ▶ Same Labeling Requirement
- ▶ Same Ingredient Requirement

Zosyn® Reformulation

Zosyn®

- **Zosyn® is an intravenous antibacterial product that contains a combination of:**
 - ▶ Piperacillin, a beta-lactam antibiotic; and
 - ▶ Tazobactam, a beta-lactamase inhibitor
- **Approved in 1993**
- **Used to treat moderate to severe infections, including pneumonia, skin infections, surgical infections, and abdominal infections**
- **Administered in a variety of settings, including the ICU, hospital floors, outpatient facilities, and home healthcare settings**

Reformulated Zosyn®

- Reformulated version of Zosyn® includes:
 - ▶ Eddate Disodium Dihydrate (“EDD”)
 - Added as a metal chelating agent to bind metal ions and prevent piperacillin dimer formation
 - ▶ Citric Acid Monohydrate (“citric acid”)
 - Added as a buffer to maintain proper pH and prevent piperacillin monohydrate formation

Compatibility Benefits Provided by The Reformulated Version of Zosyn®

- The original formulation of Zosyn® was not compatible with Lactated Ringer's Solution ("LRS") and two aminoglycoside antibiotics, amikacin and gentamicin
- The reformulated version of Zosyn® is compatible with LRS, amikacin, and gentamicin
 - ▶ When Zosyn® is supplied in 3.375 g per 50 mL Galaxy® containers, it cannot be co-administered with gentamicin due to the concentrations of piperacillin and tazobactam in those containers

Labeling for the Reformulated Version of Zosyn® is Different from the Original Labeling

- **The labeling for reformulated Zosyn® reflects the new compatibilities and conditions of use**
- **LRS**
 - ▶ The old labeling warned that LRS was not compatible with Zosyn®
 - ▶ The new labeling specifically states that LRS is a compatible diluent for Zosyn®
- **Amikacin and Gentamicin**
 - ▶ The old labeling contained warnings against the co-administration of Zosyn® with all aminoglycosides
 - ▶ The new labeling states that Zosyn® may be co-administered with amikacin and gentamicin via Y-site infusion and provides related administration information

Wyeth's Risk Minimization Program

- During the brief transition from the old version of Zosyn® to reformulated Zosyn®, Wyeth implemented a risk minimization program to help practitioners differentiate between the two formulations in light of the different conditions of administration
- Detailed communication program
 - ▶ Experienced sales force of approximately 425 representatives with targeted materials for nurses, physicians, and pharmacists
 - ▶ Direct mail and e-mail to nurses, physicians, and pharmacists
 - ▶ Specialized packaging to nurses, physicians, and pharmacists

Clinicians are Using The Reformulated Version of Zosyn® Differently than the Old Version

- In a 2007 survey commissioned by Wyeth, nurses reported extensive co-administration of reformulated Zosyn® with LRS and with gentamicin or amikacin
 - ▶ 43% of patients who received both reformulated Zosyn® and LRS received them simultaneously
 - 83% of nurses had patients within the last three months who had received both Zosyn® and LRS
 - ▶ 46% of patients who received both reformulated Zosyn® and either gentamicin or amikacin received them simultaneously
 - 95% of nurses characterized the new compatibility of reformulated Zosyn® with gentamicin and amikacin as an improvement
 - See Wyeth Supplement to Zosyn® Citizen Petition, Docket No. 2006P-0173 (June 8, 2007)

MEDICATION ERRORS

Generic Products that Differ from the Reformulated Version of Zosyn® Raise Serious Patient Safety Issues

- **Generic piperacillin/tazobactam products that are different from reformulated Zosyn® with respect to compatibility and methods of use will likely result in medication errors**
- **As stated by Dr. J. Lyle Bootman, “In sum, concurrent availability of non-interchangeable forms of the same drug poses a risk to the public health due to the drugs’ different drug interactivity profiles.”**
 - ▶ Submission by Dr. Bootman to Wyeth’s Zosyn® Citizen Petition, Docket No. 2006P-0173 (March 26, 2007)
 - ▶ Dr. Bootman is a leading authority on medication errors
 - Co-chaired the Institute of Medicine’s Committee on Identifying and Preventing Medication Errors

Medication Errors Are Real

- **It is estimated that medication errors result in 7,000 deaths each year in hospitals alone**
 - ▶ FDA Consumer Magazine, "Make No Mistake: Medical Errors Can Be Deadly Serious" (Sept. – Oct. 2000) (citing "To Err is Human: Building a Safer Health System" (IOM 1999))
 - ▶ Many of these deaths are completely preventable
- **Institute of Medicine has identified different formulations of the same drug as one cause of medication errors**
 - ▶ For example, the IOM report "Preventing Medication Errors" (2006) cites to the different marketed versions of the intravenous drug amphotericin B as having the potential to cause errors (p. 276)
 - ▶ Subsequently, in November 2007, there were indeed several deaths in the U.K. due to confusion and accidental substitution between different amphotericin B products (FDA Patient Safety News, "Avoiding Dangerous Mixups Between Amphotericin B Formulations" (Nov. 2007))

Confusion Regarding the Different Products Could Have Serious Public Health Implications

- **Serious adverse events can result if a generic product based on the old version of Zosyn® is used in a manner that is proper for the reformulated version of Zosyn® but not the old version**
 - ▶ Deactivation of piperacillin and excessive particulates
 - ▶ Deactivation of amikacin and gentamicin
- **Subpotent dosing from drug deactivation is a significant concern as Zosyn® is used to treat serious infections**
- **As indicated in the survey of nurses, reformulated Zosyn® is being used differently than the old formulation**
 - ▶ An estimated 83,000 patients received reformulated Zosyn® simultaneously with LRS, amikacin or gentamicin in 2007
 - ▶ The reformulated version of Zosyn® was simultaneously administered with either amikacin or gentamicin an estimated 280,000 patient days in 2007

Generic Labeling is Not Sufficient to Prevent Medication Errors

- **Healthcare providers assume generic drugs are the same as brand name drugs**
 - ▶ FDA's own public education materials describe a generic drug as "a copy that is identical to a brand-name drug in . . . how it is taken, quality, performance, and intended use." (FDA Publication, "Generic Drugs: What Everyone Should Know" (Aug. 2, 2004))
- **As Dr. Bootman concludes, different labeling for the generic products will probably not prevent medication errors and may actually contribute to them by providing a false sense of security**
 - ▶ "In my view, this reliance on detail buried in the lengthy product prescribing information is exactly the sort of labeling problem that leads to medication errors." (Submission by Dr. Bootman to Wyeth's Zosyn® Citizen Petition, Docket No. 2006P-0173 (March 26, 2007))

The Concurrent Marketing of Different Piperacillin/Tazobactam Products Would Require Risk Minimization

- FDA has the opportunity and the obligation to prevent a situation that will likely result in medication errors and harm the public health
- If FDA were to approve generic products based on the old Zosyn® formulation, FDA should at least require the generic companies to implement a risk minimization program
 - ▶ Generic risk minimization programs should be robust, ongoing, and subject to periodic evaluations to ensure effectiveness
- The risks associated with the long-term concurrent marketing of generic piperacillin/tazobactam products that differ from reformulated Zosyn® can be reduced, but not eliminated, by educating healthcare providers regarding the different compatibilities and conditions of use

PARTICULATES

Particulate Matter is a Serious Safety Concern

- **Particulate matter in intravenous drug products is a serious safety concern that has been linked to adverse events such as phlebitis, injection site reactions, pulmonary distress, and even death**
 - ▶ In 2007, several neonatal deaths were linked to particulates associated with the use of the intravenous antibiotic Rocephin® (ceftriaxone) (See FDA Alert, Information for Healthcare Professionals: Ceftriaxone (marketed as Rocephin) (Sept. 11, 2007))
 - Post-marketing reports indicate that crystals formed when Rocephin® was used with calcium containing products, such as LRS
 - ▶ A publication by employees of FDA's Office of Generic Drugs states, "Harmful effects of particulate contamination are well documented both clinically and experimentally."
 - Nath et al., "Particulate Contaminants of Intravenous Medication and the Limits Set by USP General Chapter <788>," *Pharmacopeial Forum* 30(6):2272 (2004)

Commercial Diluents Vary With Respect to Characteristics that Cause Particulates

- Wyeth tested over 50 lots of commercial diluents and determined that they vary greatly in pH and metal ion content (both inter and intra batches)
 - ▶ Information not contained on the label of the commercial diluents
 - ▶ Published the results
 - See Desai et al., "Zinc Content of Commercial Diluents Widely Used in Drug Admixtures Prepared for Intravenous Infusion," *Int'l J. of Pharmaceutical Compounding* 11(5):426 (2007)
- Low pH and high metal ion content increase particulate formation in piperacillin/tazobactam products

Generic Piperacillin/Tazobactam Products Should Meet USP Standards Across All Conditions of Use

- **Generic products based on the old Zosyn® formulation must show that they meet the USP standard across the wide range of pH and metal ion content seen in commercial diluents**
 - ▶ As stated in FDA's Guidance Document, "The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labeling." (Guidance for Industry: Q8 Pharmaceutical Development (ICH May 2006) at 8)
- **In-line filter is not a viable solution**

SAME LABELING REQUIREMENT

Generic Products Must Have the Same Labeling as the Reference Product

- **Statute requires the labeling for a generic product to be the same as the labeling for the reference product**
 - ▶ Except for changes required because of a suitability petition or because the drugs have different manufacturers (21 U.S.C. § 355(j)(4)(G))
 - ▶ FDA's regulations expand the statutory exceptions to the same labeling requirement to include changes due to different formulations and changes required because of patent protection or regulatory exclusivity (21 C.F.R. § 314.94(a)(8)(iv))
- **FDA has stated that the exceptions to the same labeling requirement are narrow**
 - ▶ 54 Fed. Reg. 28872, 28884 (July 10, 1989)

The Same Labeling Requirement Ensures that Generic and Reference Products are the Same

- The same labeling provision ensures that there are no significant differences between generic and reference products that could cause confusion or affect safety
- As FDA explained in the regulatory preambles:
 - ▶ “Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals” (54 Fed. Reg. 28872, 28881 (July 10, 1989))

Generic Piperacillin/Tazobactam Will Have Different Labeling than the Reformulated Version of Zosyn®

- Generic piperacillin/tazobactam products based on the old Zosyn® formulation will have significantly different labeling than reformulated Zosyn®
- Differences in at least the following elements of labeling:
 - ▶ Drug Interactions
 - ▶ Dosage and Administration
 - ▶ Directions for Reconstitution and Dilution for Use

The Labeling Differences Violate the Statutory Requirement Regarding Same Labeling

- The labeling differences reflected in the generic products exceed the limited exceptions authorized in the statute
- The labeling differences reflect real differences in the products that can cause confusion and safety problems (*i.e.*, exactly the type of situation that the same labeling requirement was intended to prevent)
 - ▶ Not the typical labeling carve-out situation
- FDA's regulations prohibit labeling changes that make the generic product "less safe or effective than the listed drug" (21 C.F.R. § 314.127(a)(7))

SAME INGREDIENT REQUIREMENT

Generic Parenteral Products Must Have the Same Inactive Ingredients as the Reference Product

- **FDA's regulations require generic parenteral products to contain the same inactive ingredients, in the same concentrations, as the reference drug**
 - ▶ Except for preservatives, buffers, and antioxidants, which may be different as long as the differences do not affect safety or efficacy
 - ▶ Specifically, 21 C.F.R. § 314.127(a)(8)(ii)(B) states:
 - “FDA . . . 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” (emphasis added)

Generic Piperacillin/Tazobactam Products Violate the Requirement Regarding Same Ingredients

- Generic piperacillin/tazobactam products based on the original Zosyn® formulation violate FDA's requirement that generic parenteral products have the same ingredients as the reference product
- The reformulated version of Zosyn® includes EDD and citric acid
- EDD was added as a metal chelator
 - ▶ Does not fall within any of the permitted exceptions (i.e., buffers, preservatives, and antioxidants)
- Citric acid was added as a buffer
 - ▶ The generic products may not change the buffer ingredient without adequate support demonstrating that the generic products perform the same as reformulated Zosyn®

FDA Should Not Waive the Requirement Regarding Same Ingredients

- Experience with the old Zosyn® formulation demonstrates that it has particulate issues
 - ▶ EDD and citric acid were added to reduce particulate levels
 - ▶ The new ingredients also provide increased compatibility and new conditions of use as reflected in new labeling
- The regulations provide stricter formulation requirements for generic parenteral products due to the increased safety risks associated with those products
- In light of the safety and legal issues, FDA should not waive its regulatory requirements governing generic piperacillin/tazobactam products based on the old version of Zosyn®

SUMMARY

Summary

- The reformulated version of Zosyn® has lower particulate levels and expanded compatibilities
- FDA should not approve generic products based on the original Zosyn® formulation in light of the safety and legal issues raised by having generic products that are so different from reformulated Zosyn®
- If FDA does approve generic piperacillin/tazobactam products that differ from reformulated Zosyn®, then the generic companies should implement a risk minimization program that is ongoing and periodically evaluated to ensure that it is meeting its objectives

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