Do Formulation Differences between the Reference Listed Drug and Generic Piperacillin-Tazobactam Impact Reconstitution?

HaiAn Zheng, James Truong, Fred Carroll, Manjunath P. Pai

Pharmaceutical differences between the reference listed drug (RLD) and generic formulations of piperacillin-tazobactam may impact the reconstitution process for intravenous administration. This study evaluated the RLD against three generic formulations and measured their reconstitution times using a standardized process. The mean (standard deviation [SD]) reconstitution time for one generic formulation was 5.57 (1.49) min, which was 35% to 42% longer ($P < 0.002$) than that for the RLD and two other formulations. Observable microscopic differences in powder particle morphology may explain these findings.

Piperacillin-tazobactam is a β-lactam-and-β-lactamase-inhibitor antibiotic combination for intravenous injection approved by the Food and Drug Administration in 1993 and marketed as Zosyn in the United States, which serves as the reference listed drug (RLD). The original formulation of Zosyn contained no excipients, but there were concerns after reconstitution that resulting particulate matter might exceed the United States Pharmacopeia (USP) standards (1). Through a series of investigations, the manufacturer of this RLD identified the primary contributors to these aberrant larger particulates to be related to the acidic pH and presence of metal cations. These findings led to the reformulation of the RLD to include sodium citrate as a buffer agent and sodium edetate as a chelator (1). This revised formulation received U.S. Food and Drug Administration approval in 2005.

In 2009, generic formulations of piperacillin-tazobactam were introduced into the U.S. market using the original no-excipient formulation, because the revised formulation of the reference listed drug (RLD) was still under patent protection (2). The regulatory approvals were made through a waiver for “exception excipient regulations,” which covers preservatives, buffers, and antioxidants used in parenteral drug products (3). Considering this known formulation differences between the products and a history of concerns regarding particulate matter formation (4, 5), this study was performed to investigate the pharmaceutical equivalence of these products during the reconstitution process.

A total of 160 vials of 3.375 g of piperacillin-tazobactam for injection were purchased through Cardinal Health (Dublin, OH), from four manufacturers (manufacturing location): (i) Pfizer (Italy) (the RLD), (ii) AuroMedics (India), (iii) APP (Italy), and (iv) Hospira (Austria) (40 per manufacturer). Sterile water for injection (SWFI) USP (20-ml single-dose vials by Hospira) and 20-ml syringes with 20 gauge 1.5-in. needles (Becton Dickinson, Franklin Lakes, NJ), and 70% isopropanol swabs were also purchased from Cardinal Health. All reconstitution processes were performed in a certified horizontal laminar flow hood, similar to standard compounding practices within a hospital setting. Several compounding pharmacists were consulted in order to develop a standard operation procedure (SOP) for reconstitution to ensure consistency, clinical relevance, and compliance with the directions and regulatory guidelines of the manufacturers.

Up to 10 vials per manufacturer were used to pilot and develop this SOP. The four formulations were not identical in physical appearance due to differences in the vial dimensions, label size, and content appearance (Fig. 1). During SOP development, we found that the reconstitution times varied significantly for the same-lot product, which were markedly affected by the swirling motion and the process of powder wetting and aggregation. Extensive powder clumping due to aggregation at the bottom and sides of the vial increased both the length and variability in the reconstitution times (Fig. 1). To reduce both intra- and interbatch reconstitution variation, our final SOP included specifications to define swirling and tapping motions, which was consistent with a common approach used by compounding pharmacists. Therefore, tapping of the drug powder was tested and standardized in our SOP. To further reduce interoperator variability, a single investigator (J. Truong) performed all of the reconstitution procedures after the SOP was defined.

The controlled tests included the reconstitution of 30 vials per manufacturer based on the finalized SOP, as follows. The sequence for the reconstitution of all 120 vials of products was randomized. To begin reconstitution, each vial was tapped three times by hand to loosen the dry powder. According to the routine practice, 15 ml of SWFI was injected rapidly at a 45° angle into the product vial while the vial was rotated circularly to distribute the SWFI and evenly wet the solid. The timer was started as soon as all SWFI was injected. Swirling was performed by hand in a circular motion at a rate of approximately 60 to 120 rpm. The operator swirled the vial for 10 s and then stopped to observe the vial for 5 s. If powder clumps were attached to the vial wall, the operator...
this approximately 1-min (intercept) difference in time. Table 1 summarizes the reconstitution time- and key formulation-based differences between the products. As shown, no significant differences in the mean reconstitution time were noted between the Pfizer (4.13 min), AuroMedics (3.90 min), and APP (4.28 min) products. The reconstitution time of the Hospira product (5.57 min) was significantly \( (P < 0.002) \) longer than that of the other products.

All the products tested are designated “cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials” (see product inserts). However, the visual morphology of the powder indicated that one of two processes were used: (i) final products as intact cake which were freeze-dried within the vial (Pfizer and AuroMedics), or (ii) final products as loose powders that were filled after bulk drying (APP and Hospira). Between these two kinds of products, an intact cake tends to have a higher degree of porosity that facilitates better wetting, while powder filled after lyophilization can settle in the vial (6). This might decrease the reconstitution time overall as a major contributory factor. This was found to be true between the Hospira and Pfizer drug products. However, the Hospira and APP products are both loose powders, but the APP product demonstrated the shortest reconstitution time. Therefore, we further investigated the powder morphology by optical microscopy. The dry powder samples were suspended in mineral oil, USP, and examined by a Zeiss Axioskop 40 with a Motic 2300 USB microcamera and imaging software. Differences in morphology and particle size were found. The most significant difference among the four formulations was with the APP product, which had much smaller particles and better powder uniformity (Fig. 1, bottom). In contrast, the other formulations had a particulate morphology consistent with freeze-dried solids. Given that the APP, AuroMedics, and Hospira formulations do not contain excipients, the observed differences in reconstitution time are unlikely to be explained by the excipient factor relative to the RLD. Instead, a more apparent contributor to these differences is the solid powder morphology and drying process.

In summary, generic and RLD antimicrobial agents, such as piperacillin-tazobactam, may not be pharmaceutically identical or equivalent. We did not evaluate the pharmacologic differences, but emerging evidence suggests that minor differences in formulations can have the potential for therapeutic nonequivalence (7). Minor pharmaceutical differences may be measurable using reconstitution time between the RLD and generic formulations. These measurable product-based differences suggest that more precise regulatory language in the process of cryodesiccated powder designation may be necessary. Specifically, we observed that swirling without tapping the vials increased the reconstitution time, a process instruction that presently does not exist in the product labels and deserves further review. These differences should be recognized and appreciated by the infectious diseases community that performs multinational clinical trials and uses common antimicrobial agents, such as piperacillin-tazobactam, in its practice.

### TABLE 1 Comparison of reconstitution time and formulation characteristics of piperacillin-tazobactam between manufacturers

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Reconstitution time (mean [SD]) (min)</th>
<th>Formulation</th>
<th>Packaging</th>
<th>Solid form</th>
<th>Manufacturing location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer (RLD)</td>
<td>4.13 (0.68)</td>
<td>Sodium edetate, sodium citrate</td>
<td>Lyophilization stopper, molded glass vial</td>
<td>Lyophilized cake</td>
<td>Italy</td>
</tr>
<tr>
<td>AuroMedics</td>
<td>4.28 (1.13)</td>
<td>No excipients</td>
<td>Lyophilization stopper, tubular glass vial</td>
<td>Lyophilized cake</td>
<td>India</td>
</tr>
<tr>
<td>APP</td>
<td>3.90 (0.76)</td>
<td>No excipients</td>
<td>Regular stopper and molded vial</td>
<td>Loose powder</td>
<td>Italy</td>
</tr>
<tr>
<td>Hospira</td>
<td>5.57 (1.49)*</td>
<td>No excipients</td>
<td>Regular stopper and molded vial</td>
<td>Loose powder</td>
<td>Austria</td>
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* \( P < 0.002 \) relative to any other products.

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REFERENCES


