Objective: To further assess piperacillin/tazobactam (P/T) generic lots in EX-USA nations and to initiate screening of meropenem (MER) generic lots recently (2011) marketed in the USA. P/T potency results expand prior experience reported in 2008 and 2009, performed by a precise, incremental MIC assay as published by Jones et al. (2008).

Methods: An additional 15 P/T generic lots (8 manufacturers; marketed in India, Chile, United Kingdom, and Sweden) were analyzed as part of an ongoing worldwide study that now includes results from 61 generic product lots (through 12/2010). Each lot was directly compared to a reference branded lot (RBL) of P/T or RBL of a previously described and validated assay method. MER lots (Hospira and Sandoz) from the USA were also tested and compared to a Merrem reference branded lot (TM0502: expirations of lots ranged from 06/2012-02/2013).

Results: The results (in 2010) of 15 P/T generic lots supplement reports of 46 other lots tested from EX-USA nations published in 2008 and 2009. Vials ranged from 2.25-4.5 gm each and all were tested within labeled expiration dates. Ochit (3 lots), Aurobindo (1 lot), Libra (3 lots), Woodwards (2 lots), Hospira (2 lots), Sandoz (2 lots), Fresenius-Kabi (2 lots) and Stragen (2 lots) generic products were assayed. Variations compared to P/T RBL were -23% to +43% (average, ±10%; prior lot experience was -16%). USA MER generic lots (Hospira [4 lots], Sandoz [2 lots]) exhibited potencies equal to Merrem RBL, without any significant variation, see Table.

Conclusions: P/T generic lots marketed outside of the USA continue to demonstrate suboptimal activity ranging from 10% to 16% less activity when compared to the RBLs. Some lots, however, show comparable or acceptable activity. MER lots, FDA-approved for use in USA, exhibited equal activity compared to Merrem via this validated in-vitro assay method. Hospital formulary practices should consider these documented differences between lots as well as between generic and branded products when making therapeutic choices.

Introduction
Piperacillin combined with the β-lactamase inhibitor tazobactam, as a parenteral broad-spectrum antimicrobial, was approved by the United States (USA) Food and Drug Administration in 1993. The introduction of piperacillin/tazobactam into the market was coupled with numerous clinical indications. Piperacillin/tazobactam has become a very widely used β-lactam/β-lactamase inhibitor combination, generally delivered as an 8:1 ratio (4 of piperacillin and 0.5 of tazobactam every 6 h), directed by the Product Package Insert (2007). Alternative dosing vials contain 2 or 3 g of piperacillin and with corresponding 0.25 or 0.375 g of tazobactam, respectively.

The original worldwide sponsor/developer of this product (Zosyn® or Tazocin®) was Wyeth (now Pfizer Inc.) Pharmaceauticals of Philadelphia, Pennsylvania, and the patent rights to produce and market this combination now vary geographically. Generic formulations containing piperacillin/tazobactam have been approved in several global markets but have been questioned as to their potencies and clinical efficiency when compared with the branded product (Jones et al., 2008 Moet et al., 2009; Ye et al., 2006).

Problems with generic formulations related to excessive imputities and subpotent activity performance issues in various in-vitro testing systems have occurred among other β-lactam agents as well as among lots of azole antifungal agents and ganciclovir. Further, a non-leachable plasticizer/sorbent's product (Zosyn®) has been reformulated using proprietary methods to maximize quality and establish more uniform potencies.

The objective of this study was two-fold: 1) to expand the quality assurance evaluation of "nonbranded" generic piperacillin/tazobactam lots (now numbering 61 lots from 33 manufacturers) using the incremental MIC antimicrobial assay method as previously described (Jones et al., 2008), and 2) to compare 5 samples of generic meropenem available in the USA to the branded product Merrem®, all tested in 2011.

Materials and Methods

**Assay method and lots:**
An updated analysis of piperacillin/tazobactam ex-USA generic formulations (see Figure 1, prior data) was performed on 15 additional lots (8 manufacturers; Table 1). In the reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) those samples were tested by the incremental MIC assay method of Jones et al. (2008) in a broad microdilution test performed as described by the Clinical and Laboratory Standards Institute (CLSI) documents M07-A9 and M100-S22. Both microdilution tests used reconstituted product vial contents as the stock solution to prepare reference MIC panels having expanded dilution doubling dilutions over the range of 0.125 to 16 mg/L. The MIC is defined as the lowest concentration of antibiotic at which 90% of the test organisms are inhibited. The MIC dilution schedule was 32, 28, 24, 20, 16, 14, 12, 10, 8, 7, 6, 5, 4, 3, 2, 1.5, 1.25, 1.0, 0.875, 0.75, 0.625, 0.5, 0.438, 0.375, 0.313, 0.25, 0.198 mg/L and a growth control.

Four well-characterized strains were used to assay the piperacillin/tazobactam activity, each having a reference MIC dilution end point and points specified as CLSI quality control ranges: Escherichia coli ATCC 29252 at 0.125-1.0 mg/L. E. coli ATCC 35218 at 0.5 to 2 mg/L. Pseudomonas aeruginosa ATCC 27853 at 10-8 mg/ml, and Staphylococcus aureus ATCC 29213 at 0.25 to 2 mg/ml. All strains were tested in triplicate on the USP broth dilution assay and solutions, and the lowest reproducible MIC value was applied to calculations of product lot potency compared with the Zosyn® (Pfizer) contemporary reference branded lot (RBL) control. The same assay method was applied to meropenem using four strains: P. aeruginosa ATCC 27853 and three clinical isolates. The tested generic products of meropenem were marketed by Hospira (3 lots) and Sandoz (2 lots); see Table 2.

**Results**

- Prior reports for generic piperacillin/tazobactam lots marketed outside of the USA showed (Figure 1):
  - Initial report of 23 lots averaged 16% less potent than RBL.
  - Second report of 23 additional lots averaged 15% less potent than RBL.
  - Branded Zosyn® lots were only 6% less potent compared to the RBL in a reproducibility experiment.
  - This current expanded study of 15 more piperacillin/tazobactam lots (all products had ≥4 unique producers) from 8 manufacturers showed a potency compared to the RBL ranging from +3% to -23% (average, ±10%).
  - USA meropenem generic lots (Hospira [4 lots] and Sandoz [2 lots]) were equal to or partly to the RBL across all assayed products and organisms.
  - This assay technique has been used successfully to make local hospital formulary additions of generic products in Europe (Sutter, Frei and Widmer, 2011).

**Conclusions**

- Ex-USA generic piperacillin/tazobactam lots generally ranged from 10% to 16% subpotent, compared with over three reports of 61 lots compared to branded product (Zosyn®) using a simple, 4 organism reproducible in vitro assay.
- In contrast, USA generic lots of meropenem (Hospira and Sandoz) were acceptable by this in-vitro assay method.
- Some generic antimicrobials continue to be variable and suboptimal in the inhibitory activity demonstrated by this assay method. Hospitals in all parts of the world should be cautious of generic products until qualified by regulators and/or local microbiological/chemical testing.

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**References**