Air contamination, syringe contamination, and cross-contamination when using an automatic compounding device for sensitizing drugs

Abstract

Objectives: To measure cross-contamination between batches of different sensitizing drugs, contamination on the outside of compounded syringes, and drug concentrations in environmental air when using an automated compounding device.

Methods: One batch of piperacillin/tazobactam syringes followed by one batch of meropenem syringes were compounded daily for three consecutive days by one operator. For each batch two hundred syringes were filled. During each batch, three stationary air samples (two inside and one outside the compounding device), and one personal air sample were collected. At the end of the compounding process, the outside of 40 syringes was tested for drug contamination by wipe sampling. The drug compounded was checked for cross-contamination with the other drug compounded in the previous batch. Liquid chromatography tandem mass spectrometry was used for the analysis of piperacillin and meropenem.

Results: Piperacillin was measured in environmental air inside the device (8.1–335 ng/m³), outside the device (5.2–21 ng/m³), and in the personal air samples of the operator (15 and 155 ng/m³) during two batches. Meropenem was not detected during meropenem compounding. Piperacillin was found in the air samples of the operator during two batches (12 and 15 ng/m³). Meropenem was not detected in any of the air samples. The drug compounded was found on the outside of the syringes for all batches (piperacillin: 1.35–30 ng/cm²; meropenem: 0.07–0.65 ng/cm²). Piperacillin was detected on the syringes in all batches (0.56–11 ng/cm²), and meropenem in two batches (0.07 and 0.46 ng/cm²). The drug solutions show no cross-contamination with the other drug for any of the batches.

Conclusions: Cross-contamination was not found and the drug concentrations in environmental air were below the Occupational Exposure Limit of 0.1 mg/m³. The automatic compounding device meets the criteria for a safe compounding of sensitizing drugs for patient and operator.

Keywords: antibiotics; automation; drug carry-over; filling syringes; meropenem; piperacillin

Introduction

Antibiotics are used in the treatment of bacterial infections [1]. Their mechanism of action is to kill or inhibit the growth of bacteria. Side effects of antibiotics in patients are well known and include diarrhea, nausea, vomiting, rashes, itching, resistance, allergic reactions, and anaphylaxis [1].

Antibiotics are widespread used in hospitals and many healthcare workers are involved in compounding and administration of these drugs daily. Even though little is known about the adverse health effects in healthcare workers occupationally exposed to antibiotics, a few studies have reported effects that include hypersensitivity, allergic skin reactions, respiratory symptoms, but also more severe effects such as drugs resistance and anaphylactic shock [2–11]. Therefore, most regulatory agencies outline the risks implied in the handling of sensitizing drugs and the importance of avoiding cross-contamination, with special concern and awareness for the penicillin and the β-lactam antibiotics [11]. More specifically, EU guidelines and FDA guidance indicate that β-lactam antibiotics should be manufactured in dedicated facilities to avoid the risk of cross-contamination [12, 13].

When compounding sensitizing drugs, two risks should be avoided: drug carry-over between subsequent batches of different drugs (cross-contamination), and exposure of operators to these drugs. Among the antibiotics, the β-lactam antibiotics have raised special awareness due to the side effects they show as sensitizing drugs.
Threshold levels of β-lactam drugs in air below which workers will not get sensitized are hard to determine and generally, the development of an Occupational Exposure Limit (OEL) for respiratory sensitizers is based on a qualitative criterion rather than a quantitative approach [14]. The OEL is the airborne concentration of a compound to which nearly all workers can be repeatedly exposed 8 h a day, 40 h a week. In such case in which thresholds for sensitizers cannot be defined properly, it is suggested to consider the lines outlined when defining OELs for non-threshold carcinogens [15].

Following this approach, both respiratory sensitizers and human carcinogen agents are included in the Occupational Exposure Band (OEB) 5 for which the OELs are <1 μg/m³ [16]. Other guidance has established less restrictive criteria, such as the NIOSH banding criteria for air and skin sensitization, which determines the lowest exposure concentration range recommendation at band E (0.01 mg/m³) [14]. Additionally, Swedish authorities have indicated that penicillin is a sensitizing drug that may cause allergy and hypersensitivity by skin contact and inhalation and have established an OEL of 0.1 mg/m³ for penicillin as inhalable dust [17].

More recently, automated compounding systems appeared on the market as an alternative for manual compounding of intravenous drugs to improve consistency and to reduce risks and requirements associated to manual compounding [18]. However, the assessment on the use of automation in hospital pharmacy has been generally focused on its use for the compounding of hazardous drugs and not much is known about the release of antibiotics produced in Pharmacy Compounding Devices (PCDs).

Hence, the objective of this study was to measure cross-contamination and exposure of the operator when compounding two β-lactam sensitizing drugs, piperacillin (penicillin antibiotic) and meropenem, using the KIRO Fill automatic compounding device [19]. Drug carry-over between subsequent batches of piperacillin and meropenem, the release of the antibiotics to device and cleanroom air, and contamination on the outside of compounded syringes were evaluated by measuring the antibiotics in compounded solutions, in air samples, and in surface wipe samples, respectively.

Materials and methods

The study was led by Exposure Control Sweden AB (Bohus-Björkö, Sweden).

Compounding device tested

KIRO Fill (Kiro Grifols S.L., Arrasate, Spain) is an automated PCD for non-hazardous sterile preparations that shall be installed in a cleanroom and operated by qualified operators [19]. The device is integrated in a horizontal laminar airflow cabinet which provides a Grade A/ISO Class 5 environment to the loading top (upper working area) and the compounding area (lower automated drug transfer area) (Figure 1).

Figure 1: KIRO Fill compounding device. 1. Loading Top (upper working area). 2. Compounding Area (lower automated drug transfer area).

During the automated aseptic compounding, two robotic units manipulate two syringes for the transfer of drug dilutions from a bulk solution in a source bag to the final preparation syringes, which are held in the upper part by means of syringe adaptors where the operator loads and unloads the syringes while the automatic compounding proceeds in the lower part of the device. Once the syringes are filled, they are automatically capped.

The automated compounding process works in runs of 20 syringes of the same drug with onscreen instructions being provided to the operator for the loading of empty syringes and caps, and for the unloading of filled and capped syringes. These runs are repeated, and the adapters reused until the batch planned for a specific day or shift is completed. At the end of each batch the compounding device is disinfected following the onscreen instructions to wipe surfaces of the areas and elements of KIRO Fill with 70 % Isopropyl Alcohol (IPA). Thereafter, the device will be ready to compound a new batch using new disposables.

Study design

Piperacillin/tazobactam and meropenem were selected for monitoring representing β-lactam antibiotics with different physical and chemical properties. Results may vary between the drugs considering the low stability of meropenem.

Three batches of 4 g/0.5 g piperacillin/tazobactam and three batches of 1 g meropenem were compounded by a qualified operator on three consecutive days (Days 1–3). On each day, the first batch was 4 g/0.5 g piperacillin/tazobactam (Batch 1) and the second batch was 1 g meropenem (Batch 2). In each batch, two hundred 50 mL BD Plastipak Luer lock syringes were filled with 20 mL of drug using the compounding device.

For the 4 g/0.5 g piperacillin/tazobactam batches, two hundred vials of 4 g/0.5 g piperacillin/tazobactam were reconstituted using 20 mL of water for injection as diluent. After reconstitution, they were pooled.
in a source bag (final concentration: 200 mg/mL) using the semi-automated system Gri-Fill (Grifols) installed in the same cleanroom as the KIRO Fill [19]. For the 1 g meropenem batches, the same procedure was followed (final concentration: 50 mg/mL). The source bags were prepared the day before compounding and were kept refrigerated until 2 h before compounding.

During each batch, two stationary air samples inside the device (loading top and compounding area), one stationary air sample in the cleanroom, and one personnel air sample were collected to measure release of the drugs in environmental air. At the end of the compounding process of each batch, the outside surface (barrel) of 40 syringes was tested for drug contamination by wipe sampling, and a sample of the drug compounded was collected to check cross-contamination with the other drug compounded in the previous batch.

The collected samples were stored at 2–8 °C until analysis at the laboratory.

**Air sampling**

The air samples were collected with 10M samplers connected to VSS-5 Buck pumps. For personnel air sampling, the 10M sampler was attached on the protective clothing of the operator, in proximity to the breathing zone (less than 30 cm from the mouth). The sampling pump was attached to a belt around the operator's waist. For stationary air sampling, the 10M sampler, and the sampling pump were fixed at specific locations near potential emission sources: loading top and compounding area of the compounding device, and in the cleanroom one meter away from the front of the compounding device to measure potential emissions into the cleanroom (Figure 2). Total particulate matter was collected on polytetrafluoroethylene filters (Whatman, 25-mm diameter and 1.0-µm pore size). The flow rate was 2.0 L/min.

Blank cleanroom air samples were collected during the three nights before compounding to measure potential background contamination. Positive control samples (filters spiked with either drug and negative control samples (non-used filters) were also collected.

The filters were extracted in 10 mL distilled water. After extraction, a part of the extract was used for analysis.

The air samples were also analyzed on the drug not compounded to measure potential drug contamination from the previous batch.

**Surface wipe sampling**

AB Wipe Kits (Exposure Control Sweden AB, Bohus-Björkö, Sweden) for surface wipe sampling were used to measure contamination on the outside (barrel) of the compounded syringes [20].

Four prewetted paper tissues containing 34 mL distilled water were used to wipe the first 20, and the last 20 syringes of each batch. It is assumed that pooling the first 20 syringes and the last 20 syringes would provide an average contamination level of all the syringes in the batch. Total barrel surface of 40 syringes is approximately 4,800 cm². The four tissues of each batch were pooled in one container and extracted with a total volume of 100 mL distilled water. After extraction, a part of the extract was used for analysis.

The wipe samples were also analyzed on the drug not compounded to measure potential drug contamination from the previous batch.

**Drug solutions**

One mL of the drug solution of each of the first 20, and last 20 syringes from each batch was collected and pooled in one container for analyses of drug cross-contamination from the previous batch. Recovery rate was calculated, based on an expected concentration of 200 mg/mL for piperacillin and 50 mg/mL for meropenem, by measuring the concentrations of the compounded drugs after dilution of the samples to a theoretical concentration of 10 ng/mL, an appropriate concentration to be measured with LC–MS/MS. Next, the measured concentrations were multiplied with the dilution factor. The diluted solutions were directly analyzed. Concentrations below 0.15 ng/mL were considered as not detected.

**Liquid chromatography with tandem mass spectrometry analysis**

Analysis was performed on a Xevo TQ-S micro mass spectrometer combined with an Acquity UPLC H-class sample manager and quaternary solvent manager controlled by Masslynx software (Waters, Milford, USA). An Acquity BEH C18, 1.7 µm, 2.1*100 mm separation column (Waters, Milford, USA) operated at 40 °C was used for gradient separation of piperacillin and meropenem with a flow of 0.35 mL/min. Elution started with a composition of 100 % solvent A (100 % MilliQ RO-water with 0.1 % formic acid) and 0 % solvent B (100 % acetonitrile with 0.1 % formic acid) with a delay of 2 min. Between 2 and 7 min, the composition changed to 100 % B and from 7.5 min starting conditions were restored. Total runtime was 11 min, and the injection volume was 8 µL. The mass spectrometer was operated with a capillary voltage of +3 kV, a desolvation temperature of 500 °C and a nitrogen flow of 1.100 L/min. Cone gas flow was set at 50 L/min (nitrogen). Argon was used as collision gas.

Retention times (RT) and MRM transitions were for meropenem: RT 4.38, Quan 384.15>141.08, Qual 384.15>159.79. All transitions were measured in positive mode. Both drugs have a linear calibration curve up to 100 ng/mL, and a detection limit of 0.15 ng/mL. Accuracy is >90 %.

**Results**

**Cross-contamination of the drug solutions in the compounded syringes**

The concentrations of the drug solutions used for compounding were 200 mg/mL for piperacillin, and 50 mg/mL for meropenem. The concentrations in the compounded syringes
were 168–169 mg/mL for piperacillin, corresponding to a recovery rate of 84–85% (Table 1). For meropenem, the concentrations were 20–23 mg/mL corresponding to a recovery rate of 40–46%. The results show low stability for piperacillin and a substantial lower stability for meropenem.

The drug solutions show no cross-contamination with the other drug as the measured concentrations were all below the detection limit (<0.15 mg/mL).

**Air samples**

Air samples were collected during compounding. Different sampling times were registered due to different compounding times of the batches (Table 2). For comparison, the measured air concentrations were converted into Time-Weighted Averages (TWAs) over 8 h. The TWAs were calculated by multiplying the measured air concentration (ng/m³) by the corresponding time-weighted average over 8 h.

**Table 1:** Cross-contamination with piperacillin and meropenem of the drug solutions in the compounded syringes.

<table>
<thead>
<tr>
<th>Day</th>
<th>Batch</th>
<th>Number of syringes a</th>
<th>Concentration, mg/mL</th>
<th>Recovery rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Piperacillin</td>
<td>Meropenem</td>
</tr>
<tr>
<td>1</td>
<td>Piperacillin</td>
<td>40</td>
<td>169</td>
<td>No previous batch</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>ND</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Piperacillin</td>
<td>40</td>
<td>168</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>ND</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Piperacillin</td>
<td>40</td>
<td>168</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>ND</td>
<td>23</td>
</tr>
</tbody>
</table>

ND: Not Detected (<0.15 ng/mL). aFirst 20 and last 20 syringes of the compounded batch.

**Table 2:** Piperacillin and meropenem in air samples.

<table>
<thead>
<tr>
<th>Sampling location</th>
<th>Day</th>
<th>Batch</th>
<th>Sampling time, min</th>
<th>Air concentration, ng/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Cleanroom</td>
<td>1</td>
<td>Piperacillin + Meropenem</td>
<td>325</td>
<td>5.2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Piperacillin + Meropenem</td>
<td>240</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin + Meropenem</td>
<td>243</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Loading top</td>
<td>1</td>
<td>Piperacillin</td>
<td>110</td>
<td>118 (27)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Meropenem</td>
<td>120</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>95</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>94</td>
<td>335 (66)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>99</td>
<td>ND</td>
</tr>
<tr>
<td>Compounding area</td>
<td>1</td>
<td>Piperacillin</td>
<td>114</td>
<td>61 (14)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Meropenem</td>
<td>125</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>95</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>104</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>112</td>
<td>8.1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>112</td>
<td>ND</td>
</tr>
<tr>
<td>Operator</td>
<td>1</td>
<td>Piperacillin</td>
<td>117</td>
<td>155 (38)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Meropenem</td>
<td>118</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>95</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>97</td>
<td>15 (3)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>88</td>
<td>15 (3)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meropenem</td>
<td>98</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Cleanroom blank (Night before Compounding)</td>
<td>1</td>
<td>Piperacillin</td>
<td>470</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Meropenem</td>
<td>720</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Piperacillin</td>
<td>670</td>
<td>ND</td>
</tr>
<tr>
<td>Control samples (ng/ml extract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control: Non used filter (n=2)</td>
<td></td>
<td>Piperacillin</td>
<td>9.3</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>10.5</td>
<td>ND</td>
</tr>
<tr>
<td>Positive control: Filter spiked with Piperacillin (n=2)</td>
<td></td>
<td>Piperacillin</td>
<td>9.3</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>10.5</td>
<td>ND</td>
</tr>
<tr>
<td>Positive control: Filter spiked with Meropenem (n=2)</td>
<td></td>
<td>Piperacillin</td>
<td>2.2</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>5.5</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: Not Detected. aValues in brackets are the corresponding calculated time-weighted averages over 8 h.
by the sampling time as percentage of an 8-h working day (480 min).

During piperacillin compounding, the drug was detected in device, cleanroom, and personnel air samples on Day 1 and Day 3. Piperacillin was detected on the loading top (118 and 335 ng/m³) and inside the compounding area (8.1 and 61 ng/m³) of the device, in the air of the cleanroom (5.2 and 21 ng/m³) and in the personnel air samples (15 and 155 ng/m³). Contamination with meropenem was not found in air samples for any of the three batches.

During the compounding of the meropenem batches, the drug was not detected in device, cleanroom, or personnel air samples. However, on Day 2 and Day 3 contamination with piperacillin was found in the personnel air samples (12 and 13 ng/m³).

Piperacillin and meropenem were not detected in the cleanroom blank samples collected during the three nights before compounding. The positive control samples contained piperacillin and meropenem and the negative control samples did not.

### Contamination on the outside of compounded syringes

Contamination with the compounded drug was found on the 40 syringes for all six batches (piperacillin: 1.35–30 ng/cm²; meropenem: 0.07–0.65 ng/cm²) (Table 3). Cross-contamination was also observed. Piperacillin was detected on the meropenem syringes for all batches (0.56–11 ng/cm²) and meropenem was measured on the piperacillin syringes of two batches (0.07 and 0.46 ng/cm²).

### Discussion

The analysis of the drugs solutions shows no cross-contamination with the other drug from the previous batch indicating that the use of KIRO Fill when compounding batches of different drugs does not involve a risk of drug carry-over between batches. The concentrations in the syringes were lower than the concentrations of the drug solutions used for compounding indicating a low stability for piperacillin but especially for meropenem. Stability in aqueous solutions has been described for meropenem and piperacillin showing the lowest stability for meropenem [21, 22]. Piperacillin was detected in environmental air during two batches indicating release of the drug during compounding. Piperacillin was detected in the device air (loading top and compounding area), in cleanroom air, and in the air around the operator. Small amounts of drugs could have been released during the transfer of the drug because just before capping, the luer-lock tip of the syringe is for a few seconds in contact with the horizontal airflow of the device. In contrast, meropenem was not detected in any of the air samples collected. This could be explained by a lower concentration of the compounded drug (50 mg/mL for meropenem vs. 200 mg/mL for piperacillin) and by a lower drug stability (recovery rates of 40–46 % for meropenem vs. 84–85 % for piperacillin).

Both aspects could have resulted in meropenem concentrations below the detection limit of the analytical method.

As far as we know, an official OEL for piperacillin has not been published. As piperacillin is a penicillin type of drug, one may use the penicillin OEL as more or less the same adverse health effects might be expected [17]. To compare the measured air concentrations with the OEL for penicillin, the concentrations were corrected into Time-Weighted Averages (TWAs) over 8 h (Table 2). The results show that all TWA-corrected air concentrations for piperacillin are far below the penicillin OEL of 0.1 mg/m³. Alternatively, if OELs are not available, one may also use OEBs [16]. As both drugs are respiratory and skin sensitizers, it is obvious to classify them in OEB E with a corresponding air concentration ≤0.01 mg/m³ [14].

Even according to the OEB classification, the TWA-corrected concentrations for piperacillin are far below 0.01 mg/m³.

Contamination with the compounded drug, and cross-contamination with the other drug was found on the surface of the syringes for all batches compounded in the KIRO Fill. The contamination may have been generated by drug residues remaining on the surfaces of the adaptors that hold the syringes during the automatic filling process. During the study, the same adaptors were used for both batches on each day. To avoid contamination on the syringes, it is recommended to replace the adaptors for each batch and to clean them thoroughly after use.

Limitations of the study concern drug stability and sampling of the compounded syringes. Lower drug stability for meropenem compared to piperacillin could explain the non

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**Table 3**: Piperacillin and meropenem on the outside of compounded syringes.

<table>
<thead>
<tr>
<th>Day</th>
<th>Batch</th>
<th>Number of syringes</th>
<th>Contamination, ng/cm²</th>
<th>Piperacillin</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperacillin</td>
<td>40</td>
<td>1.35</td>
<td>No previous batch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>0.56</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Piperacillin</td>
<td>40</td>
<td>2.50</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>11</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Piperacillin</td>
<td>40</td>
<td>30</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>40</td>
<td>10</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

*First 20 and last 20 syringes of the compounded batch.*
detectable air concentrations and the low contamination on the outside of the compounded syringes. One may also debate the small number of compounded syringes tested and how they were selected. Pooling the first 20 and the last 20 syringes is not considered as a randomized selection. However, testing 20% of the syringes including the first 20 and last 20 syringes will at least give a reasonable indication of the contamination on the outside of the syringes.

The study did not compare robotic compounding to other compounding methods. Further studies should assess the benefit of automated compounding compared to semi-automated or manual compounding methods regarding cross-contamination and risk of exposure for operators to \( \beta \)-lactam antibiotics. This should include all operator actions additional to the compounding process such as loading, unloading, and the preparation of source bags that can contribute to the transfer of chemical contamination.

The results show that the measured contamination in the air and on the surface of the compounded syringes, has not resulted in cross-contamination of the drug solutions in the ready to administer syringes. The results demonstrate that the automatic compounding of sensitizing drugs in KIRO Fill ensures patient’s safety by avoiding cross-contamination of drugs in subsequent compounded batches. This is relevant to avoid adverse reactions in patients with hypersensitivity to \( \beta \)-lactam antibiotics and other drugs. In addition, operator’s safety is guaranteed as the drug levels measured in environmental air are below the OEL indicating compounding of sensitizing drugs can be performed in the absence of isolator systems. Nevertheless, when compounding sensitizing drugs, operator’s exposure should be avoided as much as possible. This includes the use of personnel protective equipment.

**Research ethics:** Not applicable.

**Informed consent:** Informed consent was obtained from the operator (Andrea Alcorta) included in this study.

**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Andrea Alcorta, Naiara Telleria, and Jaione Grisaleña were employed at Kiro Grifols S.L., manufacturer of the compounding device studied. Gerardo Cajaraville is an advisor to Kiro Grifols on subjects not related to the scope of this study. Paul Sessink, Maria José Tamés and Ana Riestra have no conflicts of interest to declare.

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**References**


