International Journal of Pharmaceutics 485 (2015) 160–163

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Personalised medicine

Multiple withdrawals from single-use vials: A study on sterility

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ARTICLE INFO

Article history:
Received 30 January 2015
Accepted 5 March 2015
Available online 9 March 2015

Keywords:
Single-use vial
Drug packaging
Drug storage
Disposable equipment
Drug contamination
Syringes/microbiology

ABSTRACT

Background: Reutilization of single-use vials containing medical drugs is still under discussion. This practice has been adopted as a standard to avoid drug wastage, particularly in developing countries and in the aftermath of disasters. Some studies have assessed sterility of medications stored in single-use vials after utilization as multiple doses; however, most of these were limited to one single drug, included a low number of samples and did not consider an intermediate transfer step from the vial to a disposable syringe. The purpose of this study was to assess microbial contamination of samples withdrawn over three days from disposable syringes prepared from single-use vials.
Methods: A prospective sterility study was conducted. A total of 600 initial samples were prepared from six-hundred 10 mL single-use vials of physiological solution into six-hundred 20 mL disposable syringes. Samples were prepared in three different standard operating rooms, on six different days and by the same operator, using basic sterile technique. All syringes were capped, placed together in a non-sterile steel container, covered with a clean drape and stored in the refrigerator at 4° C under non-sterile conditions. Using basic sterile technique, four samples were withdrawn daily and cultured from each syringe over the next 3 days. Microbial growth was examined on Sabouraud agar and chocolate agar culture media.
Results: A total of 7200 samples were collected and 14,400 cultures were performed. No evidence of microbial growth in any of the culture media plates was found.
Conclusion: This study demonstrated that contents initially stored in single-use vials and subsequently transferred into disposable syringes in an operating room using sterile technique, maintain sterility after 4 withdrawals per day for a total of 3 days.

1. Introduction

Ever since their first use in daily practice, reutilization of drugs contained in single-dose/use vials (SUVs)[1] has been widely discussed (Stokowski, 2014). In its latest statement, the Center for Disease Control and prevention (CDC, 2011, 2012)[2] reaffirmed that "*Vials that are labeled as single-dose or single-use should be used for a single patient and single case/procedure/injection.*" This assertion relies on the fact that SUVs contain neither antimicrobial agents nor preservatives and, therefore, contamination should be expected after initial vial entry. However, several studies have demonstrated that health professionals often do not comply with CDC recommendations (Stokowski 2014). For instance, the survey conducted by Woodbury et al. (2014) among anesthesia providers in Atlanta, showed that close to 60% admitted to having re-used SUVs for different patients. Similarly, Baniasadi et al. (2013) conducted a study in Iran in which 205 opened vials stored in

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[1] SUV: single-dose/use vials.

[2] CDC: Center for Disease Control and Prevention.

http://dx.doi.org/10.1016/j.ijpharm.2015.03.010
0378-5173/

different hospital wards were analyzed; of these, 80.49% were SUVs employed as multiple-use vials.

Re-using SUVs has been adopted by health care providers as standard practice especially in developing countries, in the aftermath of disasters, or in complex humanitarian emergencies in an attempt to avoid drug wastage. For instance, although in the International Standards for a Safe Practice of Anesthesia (Merry et al., 2010) morphine and pethidine are both considered as mandatory medications, Hodges et al. (2007) found that among anesthesia practitioners in Uganda only 45% had uninterrupted access to this particular drugs. Often in these settings, the shortage of medications is not only a consequence of restrictive laws but also of high drug prices in comparison to Western health-care systems.

The CDC recognized the motivations leading health providers to reutilize the contents of SUVs for more than one patient, and therefore an option was extended for the storage of contents of unopened SUVs into multiple-use syringes. However, this repackage procedure must be performed exclusively by qualified personnel and under specific conditions complying with the US Pharmacopeia (USP)[3] 797 standards (Stokowski, 2014), for instance, in pharmacies. Consequently, operating rooms and other clinical areas are considered inadequate environments for splitting and repacking vials regardless of the technique used (Stokowski, 2014).

In recent years, some studies have been conducted to assess sterility of different medications stored into SUVs and used as multiple doses (Ornek et al., 2008; Reiter et al., 2003). However, most of these were restricted to a single drug, included a low number of samples and did not consider transferring contents into disposable syringes, a maneuver frequently performed when the dosage needed per patient is much lower than the total amount of drug contained in a single vial.

Therefore, the purpose of this study was to determine microbial contamination of multiple samples withdrawn during several days from disposable syringes prepared from SUVs. The expected result was that contamination rate among all samples would not exceed that calculated for simple filling of syringes under the same environmental conditions (Stucki et al., 2009).

2. Materials and methods

2.1. Study setting

Samples were prepared from SUVs filled with physiological solution (PS)[4] in three different standard operating rooms (International Organization for Standardization-ISO Class 7),[5] (Cleanroom Cleaning Product Guide, 2014) on six different days, upon conclusion of all elective surgeries, and by the same operator (Fig. 1). The operator was a senior anesthetist, well-trained in the sterile preparation of drugs. Samples were prepared using exclusively basic principles of asepsis: hand-washing, mask, cap, sterile gloves and a sterile sheet. Air particulate contamination was not assessed in any of the three different operating rooms.

2.2. Power analysis and statistics

Considering a 95% confidence interval for the proportion of contaminated samples, with a margin error of ±4%, we initially prepared 600 syringes to test. Sample size calculations were performed using the Statistics Calculator software (nQuery Advisor, v5.05).

2.3. Sample preparation and storage

A total of 600 samples were prepared into 20 mL disposable syringes from six-hundred 10 mL SUVs filled with PS (Fig. 2). The total volume was extended to 20 mL with additional PS to simulate drug dilution. All syringes were then capped with their needle, placed together in a non-sterile steel container, covered with a clean non-sterile drape and stored in the refrigerator at −4° C (Fig. 3). Using sterile technique, four samples were withdrawn daily from each syringe and cultured during the next 3 days (Fig. 4) yielding a total of 7200 samples to be examined for sterility.

2.4. Microbiological analysis

10 μL from each sample were cultured into Sabouraud agar and chocolate agar media according to the Difco & BBL Manual, BD guidelines for culture media (Difco and BBl Manual, 2014). Culture media plates were incubated at 30–37 °C for 48 h and then checked for bacterial and yeast growth. Sabouraud media were kept at 25–30 °C for an additional 5 days to facilitate growth of filamentous fungi. Microbial contamination was defined in CFU/plate.[6] Growth on the main inoculation site was considered significant. All cultures were performed by the same microbiologist.

Both chocolate and Sabouraud culture media were received along with the manufacture's Declaration of Conformity with the European In Vitro Diagnostic Directive. Media for microbial growth were validated with a promotion test according to the United Kingdom National External Quality Assessment Service for Microbiology[7] (UK NEQAS) guidelines (UK NEQAS, 2014) by inoculating 0.1 CFU/μL of *Escherichia coli*,*Staphylococcus epidermidis* and *Candida albicans*. Positive growth was considered superior or equal to 10 CFU/plate. The same quality control procedure was performed at the opening of each new media lot.

3. Results

A total of 7200 samples were collected. Overall, 14,400 cultures (7200 for bacteria and 7200 for fungi) were performed. No evidence of microbial growth in any of the culture media plates was found at the end of the observational period.

4. Discussion

To the best of our knowledge, this is the first attempt to systematically assess microbial contamination of SUVs after content withdrawal, dilution, storage and subsequent multiple withdrawals performed during several days. Our findings suggest that if initial withdrawal from SUVs into disposable syringes is performed in a standard operating room with sterile technique, and if syringes are stored under refrigeration, sterility is preserved for at least 3 days when four withdrawals per day are performed.

It is remarkable that, even though samples were prepared in three different operating rooms at the end of all planned surgeries, and therefore with increased possibility of environmental contamination, no microbial growth was detected. Supporting our findings, Stucki et al. (2009) assessed contamination of syringes filled in different environments (horizontal laminar-airflow, cleanroom, operating room and ward) after different risk

[3] USP: US Pharmacopeia.
[4] PS: physiological solution.
[5] ISO: International Organization for Standardization.
[6] CFU: colony forming unit.
[7] UK NEQAS: United Kingdom National External Quality Assessment Service for Microbiology.