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Pharmaceutical quality of eight generics of ceftriaxone preparation for injection in Eastern Asia

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Objectives: To compare the pharmaceutical quality of original and generic ceftriaxone sodium preparations for injection produced in Eastern Asia.
Methods: Standard physical and chemical laboratory tests were performed.
Participants/material: Ceftriaxone (Rocephin®, Roche, Switzerland) was the reference material. Generics produced in China, India, and Indonesia were sampled in China and Myanmar within their expiration dates.
Results: Eight generics obtained from Eastern Asia markets in January 2013 were analysed. All eight generics failed the specifications in three or more tests. Residues of solvents and metals were detected in all generics, four were not particle free, and two were not sterile.
Conclusions: All tested generic ceftriaxone products failed to meet the pharmaceutical quality standards of the branded original. The high levels of impurities and the identified contamination of particles and residues are of clinical concern, as they could impact tolerability and safety in patients in need of an effective parenteral antibiotic.

Keywords: Ceftriaxone, Rocephin, Pharmaceutical quality, Generics, Eastern Asia

Introduction

Ceftriaxone is a broad-spectrum bactericidal agent that belongs to the third-generation cephalosporins. It was patented, manufactured, and marketed in 1982 as Rocephin® (Roche Pharmaceuticals, Basel, Switzerland) and is active *in vitro* against a wide range of Gram-positive and Gram-negative organisms, which include beta-lactamase producing strains. Ceftriaxone is administered intravenously or intramuscularly in a once-daily schedule due to a long elimination half-life.[1] It is indicated in bacterial meningitis, pneumonia, acute otitis media, intra-abdominal infections, complicated urinary tract infections, infections of bones and joints, complicated skin and soft tissue infections, the sexually transmitted infections: gonorrhoea and syphilis, and bacterial endocarditis.[2] Ceftriaxone is listed by the WHO as an essential medicine.[3]

Since the expiration of Rocephin patent in Europe in 2000 and in North America in 2005, generic products are available in many countries. For generics, efficacy and safety are guaranteed by proof of bioequivalence between generic and innovator product.[4] For parenteral (or nonabsorbed) formulations, however, therapeutic equivalence is assumed from pharmaceutical equivalence (i.e. demonstration of equivalent amounts of the same active pharmaceutical ingredient (API) between generic and innovator product), given that delivery of the API occurs directly in the systemic circulation (complete bioavailability) unlike oral (or absorbed) formulations that first undergo metabolism. As a consequence, regulatory authorities can waive the requirement for generic nonabsorbed antibiotics to demonstrate therapeutic equivalence with the innovator branded product,[5] as long as they are administered as an aqueous solution.[6] Several studies have compared original and generic versions of ceftriaxone and observed that many generics failed to meet the quality standards of the branded product[7,8] and others predicted an insufficient achievement of the time above minimal inhibitory concentration (MIC) and thus reduced efficacy, increased risk of clinical failure, and/or increased risk of emergence of resistant isolates for the generics.[9]

Many countries in Asia are confronted to cost pressure in their healthcare systems, mainly due to an ageing population (China including Hong Kong, Japan, Singapore, and South Korea) or inversely due to fast-growing and younger populations (India, Indonesia, Malaysia, Pakistan, and Philippines).[10] To contain drug expenditure, many states develop

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legislation to encourage prescribing of generic medicines. Non-proprietary agents like generics often cost several times less than the innovator branded product. They can drastically reduce the cost of care, and their origin from different sources improves guarantee of supply. The Indian pharmaceutical industry evolved to become one of the world's leading suppliers of low-cost generic drugs.[11] As a consequence, Asia's markets are dominated by low cost and locally or regionally manufactured generic medicines. Therefore, it is likely that hundreds of thousands of patients are exposed to generic ceftriaxone for the treatment of potentially life-threatening infections. To date, no analyses have been reported for ceftriaxone generics manufactured in Asia. The current study compares the pharmaceutical quality of the latter with the original branded product. Analysis was performed according to European Pharmacopoeia and to the standard physical and chemical laboratory tests developed and routinely practiced at Roche facilities. All tests were conducted in GMP-regulated Quality Control and Development Laboratories of F. Hoffman-La Roche in Basel, by qualified personnel. Values of reference were the official Roche specifications for product testing at release.

Method

Generic products

Generics of ceftriaxone 1000 mg injectable formulations manufactured in China, India, Indonesia, and Taiwan were sampled from approved commercial supply channels in China and Myanmar within their expiration dates. The sampled generics represent the largest proportion of ceftriaxone 1000 mg injectable formulations used in China and Myanmar according to local market data.

Pharmaceutical quality tests

A total of 19 qualitative and quantitative tests were performed. They concerned the vial (container integrity), the vial content (colour and crystallinity of powder, filling content), the reconstituted solution (colour, opalescence, presence of visible and sub-visible particles, pH value, identity and content of API, content of related substances, residual solvents, and metals), sterility, and microbiology.

Physical container closure integrity

The vials were reconstituted (12% solution) after immersion in a methylene blue dye bath. The presence of a blue colouration was visually assessed.

Colour of vial content and of reconstituted solution

Colour of vial content was assessed visually according to the standards described in the 'Munsell Book of Colour.'[12] Colour of a 12% aqueous solution was assessed in a 5 ml colourless test tube against a white background and compared to the European Pharmacopoeia Colour Scale.[13] Rocephin specifications for colour are white to off-white powder, and not more coloured than Y9, YG9, or OY9 for the reconstituted solution.

Crystallinity and electron microscopy

Crystallinity was assessed by microscope (Leica DM6000®, Wetzlar, Germany) with polarization filters and magnification $\times 100$. The powder was gold coated for 15 seconds (Leica Gold coater EM SCD050, Wetzlar, Germany) for electron microscopy (FEI® Quanta FEG 250, Eindhoven, Netherlands). Images were obtained in high vacuum, at voltage 2 kV, and magnifications $\times 300$ and $\times 2000$. Rocephin specification is crystalline powder.

Filling content

Five containers without labels and metal caps were weighted individually, then emptied, rinsed with water and ethanol, dried at 105°C for 1 hour, cooled, and weighed again. The weight difference was recorded and averaged. Rocephin specification for fill mass is 1140–1284 mg.

Visible and sub-visible particles in the reconstituted solution

Ten vials were reconstituted with 10 ml water and placed for 2 minutes in a particle-free environment, i.e. laminar flow unit equipped with HEPA filter, until complete dissolution of the powder. Observation was performed in a dark field mode (OPTIMA® lamp) with polarization filter and magnification $\times 2$ for visible particles, and with a liquid particle counting instrument (HIAC 9703 Royco®) for sub-visible particles. Rocephin specification is maximally six visible particles per container and maximum 20 per 10 containers, and maximum 600 sub-visible particles ≥ 25 μm per container.

Opalescence

Opalescence was measured with a turbidimeter (Hach® 2100AN, Düsseldorf, Germany) after dissolution of 6.0 g of powder in 50 ml water and filtration by 0.8 μm filter. The formazin turbidity scale was used based on the European Pharmacopoeia primary opalescent suspension of 4000 FTU (formazin turbidity units).[13] A value <3.0 FTU qualifies for a clear solution.

pH value

The pH value was determined potentiometrically (Metrom 780® pH-metre, Herisau, Switzerland) according to the method described in European Pharmacopoeia.[13] Rocephin specification is a pH value of 6.0–8.0.

Identification and content of API, related substances, and degradation products

Near infrared spectroscopy was performed with intact vials (measurement through the bottom of the glass vials). The spectrum was recorded in the range of 4000–10 000/cm (Thermo® Antaris II NIR spectrometer, Madison, USA) and compared to API

reference in the spectral database. The content of active substance and degradation products was determined using high-performance liquid chromatography (HPLC) according to the method described by Lambert and Conway.[7] Rocephin specification for content of substances per vial are ceftriaxone 900–1100 mg (1000 mg±5%), related substance Ro 11–8390 maximum <1.04%, and all degradation products maximum <2.29 %.

Residual solvents

Residual solvents were analysed according to the method of the European Pharmacopoeia.[13] One microlitre of reconstituted solution (12% aqueous) was injected in a head space gas chromatography (GC) (Hewlett-Packart 6890 with flame ionization detector FID), equipped with a fused silica capillary columns of 0.32 mm internal diameter, helium flow rate of 1 ml/min, oven temperature at 90°C, and FID at 260°C. The references were cyclotrisiloxane hexamethyl-, octamethyl-, and decamethyl-; tetradecan; hexadecan; butylated hydroxytoluene (BHT); and nonadecane.

Metals

Metals were determined by X-ray fluorescence spectroscopy (SPECTRO X-Lab 2000 XRF spectrometer). Ten grams of powder was analysed in a polypropylene beaker closed by polypropylene film. A screening test was performed from Silicon (atomic weight 28) to Uranium (atomic weight 238).

Sterility

Sterility was tested using the Steritest® membrane filtration system (Millipore, MA, USA). A solution of 10 g of substance in sterile water was membrane filtered. The membrane filters were then incubated (a) on fluid thioglycollate medium at 30.0–35.0°C and (b) on trypticase soy broth at 20.0–25.0°C. Microbial growth was checked after 3, 7, and 14 days of incubation. Forty vials per product were tested.

Microbiology

Bacterial endotoxins were determined using the quantitative kinetic-chromogenic measurement of the endotoxin concentration [limulus amoebocyte lysate (LAL)]. Three vials per product were tested. Rocephin specifications per vial are maximum 80 EU.

Results

Eight ceftriaxone generics were purchased from approved commercial supply channels in China and Myanmar in January 2013 and analysed in March–August 2013. Sources and batch numbers of the product tested are listed in Table 1.

Physical characteristics of the vials and contents

All containers were tightly closed and all generic products were white or off-white, similar to Rocephin (Table 2). All eight generic products had an amorphous appearance in contrast to the crystalline reference. The average fill mass and the API content of all generics fell within the Roche specifications.

Physical characteristics of the reconstituted solutions

Two generics manufactured in India, one in China and one in Indonesia, were not particle free. Two generics from China were not opalescent, all six others failed to meet the standards for clarity of an aqueous solution.

Impurities

All generic products met the Roche specifications for the total of degradation products. All generics showed impurities that were analysed as residual solvents and identifiable as lubricants or lubrication solvents. Residues of the metals Bromide, Iron, Manganese, Strontium, and Zinc (Br, Fe, Mn, Sr, and Zn) were detected in all generics, in quantities ranging from 1 ppm (Zn) to 16 ppm (Br).

Sterility and microbiology

Two generics from India were not sterile. *Kocuria rhizophila*, *Brachybacterium muris*, and gram-positive cocci (not further specifiable) were identified in the first generic and gram-positive sporulated rods (not further specifiable) in the second. Bacterial endotoxins were <10 EU/vial in all generic products and did not exceed the EU pharmacopoeia specifications.

Table 1 Details of generic ceftriaxone products tested

Product	Manufacturer	Manufacturing country	Purchase country	Batch nr	Manufacture date	Expiry date
Becef	Nectar Lifesciences	India	Myanmar	GBIC12011	Sep 2012	Aug 2015
Cefaxone	Lupin	India	Myanmar	CXC664A	Jul 2012	Jun 2014
Cefin	Panbiotic	Taiwan	China	1209030 (H20100294)	Sep 2012	Sep 2015
Ceftriaxon	CCPC	China	China	11912014	Sep 2012	Aug 2014
Ceftriaxon[1]	North China Pharmaceutical Co., Ltd	China	China	K1209110	Sep 2012	Aug 2014
Incept	Ind-Swift Ltd	India	Myanmar	DC2151	May 2012	Apr 2014
Oframax	Ranbaxy	India	Myanmar	2426492, 242269, 2422328	Jul 2012	Jun 2015
Triacef	Dexa Medica	Indonesia	Myanmar	4307270	Jul 2012	Jul 2015

[1]Written in Chinese only.

Table 2 Specifications of Rocephin and physical characteristics of generic ceftriaxone products tested

	Description vial/dry powder/vial						In solution						
Product (manufacturer)	Container integrity	Crystallinity	Colour	Average fill mass (mg)	Content of ceftriaxone per vial (mg)	Particles per 1/10 containers	Opalescence	pH	Degradation products	Metals	Residual solvents	Sterility	Deviations
Rocephin (Roche)	Tight closed	Crystalline	White to off-white	1140–1284	900–1100	<6/<20	Clear; <3.0	6.0–8.0	<2.29%	0	0	No growth	0
Becef (Nectar Lifesciences)	Tight closed	*Mostly amorphous*	Off-white	1189	974	*4/23*	*Strong opalescent; 22.6*	6.9	0.52%	*Mn* Fe* Zn* Br**	*S B TH +*	No growth	5
Cefaxone (Lupin)	Tight closed	*Mostly amorphous*	Off-white	1205	969	2/10	*Opalescent; 14.2*	6.3	0.84%	*Fe* Zn* Br† Sr**	*S B TH +*	No growth	4
Cefin (Panbiotic)	Tight closed	*Mostly amorphous*	White	1195	996	*6/18*	Clear; 2.1	6.8	0.23%	*Zn**	*S B H +*	No growth	4
Ceftriaxon (CCPC)	Tight closed	*Amorphous crystalline*	White	1194	992	2/6	Clear; 2.2	6.7	0.17%	*Zn* Br**	*S B +*	No growth	3
Ceftriaxon (NCP)	Tight closed	*Amorphous crystalline*	White	1168	974	2/3	*Faintly opalescent; 3.2*	6.7	0.28%	*Fe* Zn* Br**	*S B+*	No growth	4
Incept (Ind_Swift)	Tight closed	*Mostly amorphous*	Off-white	1209	981	*8/31*	*Opalescent; 13.2*	6.5	0.64%	*Zn**	*S B TH +*	*Germs§*	6
Oframax (Ranbaxy)	Tight closed	*Mostly amorphous*	White	1170	963	3/6	*Opalescent; 7.7*	6.5	0.54%	*Fe* Zn†*	*S B TH+*	*Germs‖*	5
Triacef (Dexa Medica)	Tight closed	*Amorphous crystalline*	White	1163	941	*12/13*	*Opalescent; 6.4*	6.5	0.73%	*Fe* Zn† Br‡*	*S B+*	No growth	5

*Content 1–4 ppm;
†Content 5–9 ppm;
‡Content 16 ppm.
§*Kocuria rhizophila, Brachybacterium muris, and gram-positive cocci.*
‖Gram-positive sporulated rods.
S: siloxane; B: butylated hydroxytoluene; T: tetradecan; H: hexadecan; +: not identifiable.
Deviations are in italics.

Discussion

The eight generic products tested failed to match the Rocephin specifications in three or more tests. Residual metals and solvents were observed in all tested generic products, and four generics contained visible and subvisible particles outside the specifications. In two out of eight generics tested in this study, a microbiologic contamination could be identified. The most violations (six deviations) were observed in one generic manufactured in India. We could identify two areas of concern: particles and metal content, with corresponding potential toxicological issues, and microbiologic contamination with potential impact on efficacy and safety.

The presence of the metals Bromide (Br), Iron (Fe), Manganese (Mn), Strontium (Sr), and Zinc (Zn) in all generic products tested is of relevance, not only because Mn (Class 2), Fe, and Zn (Class 3) are listed as 'Metals with safety concerns' by the European Authorities[14] but also because these metals may be residues of process catalysts or reagents used in the manufacturing process, or represent contamination from manufacturing equipment and/or the environment. In any case and irrespective of the permitted daily exposure based on duration of treatment, administration route, and maximal daily dose,[14] the presence of metals in intravenous generic antibiotics represents a true quality issue.

Previous studies with oral formulations have found more impurities in generic products[15,16] including antibiotics[17,18] than in the innovator product. These findings demonstrated that generic tablets were often not comparable *in vitro* to the innovator product and suggested that generics were not as effective *in vivo* as innovators because of induced changes in pharmacokinetics and tolerability. In some recent studies, pharmacokinetic characteristics and antibacterial activity of original intravenous antibiotics were compared with those of generic preparations. In spite of pharmaceutical and *in vitro* microbiological equivalence, major variations in *in vivo* efficacy were observed among generic antibiotics such as vancomycin,[19] cefotaxime,[20] and gentamicin.[21] Furthermore, clinical and microbiological failures were reported with generic antibiotics,[22,23] as well as bacterial resistance.[24] Thus, even when the guidelines of drug regulatory agencies concerning bioequivalence of generics are not violated, evidence is growing that pharmaceutical equivalent generic antibiotics can be inferior *in vivo* compared to the innovator product.[25] A randomized clinical study conducted in South Africa in 63 patients with community-acquired meningitis concluded of non-inferiority of a local generic ceftriaxone product, based on drug concentration in cerebrospinal fluid.[26] However, besides methodological weaknesses (such as small patient number and significant difference in survival between the groups) and non-control for confounding factors (such as HIV positivity, degree of immunosuppression, or co-existent disease), statistically significant lower plasma levels, i.e. twofold lower trough values, were reported for the generic product compared to the branded original, indicating pharmaceutical inequivalence. In face of the emerging evidence, the US authorities planned additional *in vivo* research with generics.[27] The exact mechanism behind the observed phenomenon is still under investigation, but some experimental data suggest that contaminants and especially particles found in generics may compromise tissue perfusion and impact the microcirculation, which may be clinically relevant in critically ill patients.[20,28] As a consequence, and given the crucial importance of appropriate antimicrobial treatment in patients with life-threatening infections combined with the broad use of generic antibiotics, our results showing that half of generic products contained particles represent a potential safety issue. Further studies and efforts are needed in this field to improve public health.

The main limitation of the study is the lack of *in vivo* data. However, evidence is growing that *in vitro* contamination may directly impact *in vivo* efficacy.

The presence of microbiological contamination in injectable single-use vials before use is described in the literature. However, the reported cases concern mostly improper injection technique or multiple puncturing of single-use vials[29–31] with contamination, e.g. due to syringe re-use. A comprehensive review of 60 reports on breach of standards in infection control practice failed to show a causal relationship connecting the multipatient use of single-dose vials to infection.[32] Whatever the case may be, our findings of intrinsic microbiological contamination in two ceftriaxone generic vials represent non-sterility detected in a manufactured injectable product and is of great safety concern.

Conclusion

All tested generic ceftriaxone products manufactured in Eastern Asia failed to meet *in vitro* quality compared to the original branded product. The impurities identified as particles, residues of solvent, and metals, as well as microbiologic contamination are of clinical concern, as they could impact tolerability and safety in patients in need of an effective parenteral antibiotic. Ultimately, while generics may represent an economic relief opportunity for health care systems under pressure like in Eastern Asia, consideration needs to be given to the introduction of new standards of quality checks before and after commercialization to ensure continuous efficacy and safety of the equivalent agent.

List of Abbreviations

API active pharmaceutical ingredient
MIC minimal inhibitory concentration

FTU	formazin turbidity units
GC	gas chromatography
LAL	limulus amoebocyte lysate

Author's Information

IA is a researcher at the University of Basel specialized in adherence to medication and in developing guidelines for community pharmacies. She is a lecturer and member of several pharmacy and pharmacology societies.

Disclaimer Statements

Contributors All authors designed the study. MA and YR collected the data. IA analysed and interpreted the data. All authors were involved in drafting and revising the manuscript critically for intellectual content and gave final approval of the version to be published.

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Conflicts of interest MA, YR, and GS are employees at Roche. IA received consultant fees.

Ethics approval Not applicable.

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References

1 Richards D, Heel R, Brogden R, Speight T, Avery G. Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs. 1984;27(6):469–527.
2 European Medicines Agency EMA. Referral of the Committee for Medicinal Products for Human Use (CHMP) on Rocephin. 2014. Available from URL: www.ema.europa.eu/ema/index.jsp?curl=‴pages/medicines/human/referrals/Rocephin/human_referral_000362.jsp&mid=WC0b01ac05805c516f (last access 20 February 2014).
3 World Health Organization WHO. WHO model list of essential medicines, 18th list. 2013. Available from URL: www.who.int/medicines/publications/essentialmedicines/en/index.html (last access 28 February 2014).
4 Food and Drug Administration FDA. Drugs@FDA Glossary of Terms. Available from URL: www.fda.gov/Drugs/InformationOnDrugs/ucm079436#TE (last access 20 February 2014).
5 Snyman J. Editorial - bioequivalence: should we trust generic antibiotics? South Afr J Epidemiol Infect. 2005;20(3):78–9.
6 Japanese Pharmaceutical and Food Safety Bureau. Guideline for Bioequivalence Studies of Generic Products, Attachment 1 of Division-Notification 0229 No. 10 [translation in English]. 2012. Available from URL: www.nihs.go.jp/drug/be-guide%28e%9/Generic/GL-E_120229_BE.pdf] (last access 19 March 2014).
7 Lambert PA, Conway BR. Pharmaceutical quality of ceftriaxone generic drug products compared with Rocephin®. J Chemother. 2003;15(4):357–68.
8 Tange M, Yoshida M, Nakai Y, Uchida T. Comparison between original and generic versions of ceftriaxone sodium preparation for injection: compatibility with calcium-containing product. Chem Pharm Bull (Tokyo). 2012;60(4):429–34.
9 Schito GC, Keenan MHJ. Predicting the clinical efficacy of generic formulations of ceftriaxone. J Chemother. 2005;17(Suppl 2):33–40.
10 Donghyun P, Kwanho S. Impact of population aging on Asia's future growth. Asian Development Bank (ADB) Economics Working Paper Series, ADB, Manila, Philippines. Vol. 281. 2011. p. 1–30.
11 Kapczynski A. Engineered in India-Patent Law 2.0. N Engl J Med. 2013;369(6):497–9.
12 Munsell A. Munsell Book of Colour. New Windsor, New York: GretagMacBeter; 1996.
13 Anonymous. European Pharmacopoeia 7.0. 2011.
14 European Medicines Agency EMA. Guideline on the specification limits for residues of metal catalysts or metal reagents. Doc Ref EMEA/CHMP/SWP/4446/2000. 2008. Available from URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003586.pdf (last access 20 January 2014).
15 Smith JC, Tarocco G, Merazzi F, Salzmann U. Are generic formulations of carvedilol of inferior pharmaceutical quality compared with the branded formulation? Curr Med Res Opin. 2006;22(4):709–20.
16 Taylor PW, Keenan MHJ. Pharmaceutical quality of generic isotretinoin products, compared with Roaccutane. Curr Med Res Opin. 2006;22(3):603–15.
17 Nightingale C. A survey of the quality of generic clarithromycin products manufactured in Slovenia and Israel. Adv Ther. 2000;17(3):167–78.
18 Nightingale C. A survey of the quality of generic clarithromycin products from 18 countries. Clin Drug Investig. 2005;25(2):135–52.
19 Vesga O, Agudelo M, Salazar BE, Rodriguez CA, Zuluaga AF. Generic vancomycin products fail in vivo despite being pharmaceutical equivalents of the innovator. Antimicrob Agents Chemother. 2010;54(8):3271–9.
20 Lehr H-A, Brunner J, Rangoonwala R, Kirkpatrick CJ. Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle. Am J Respir Crit Care Med. 2002;165(4):514–20.
21 Zuluaga AF, Agudelo M, Cardeno J, Rodriguez CA, Vesga O. Determination of therapeutic equivalence of generic products of gentamicin in the neutropenic mouse thigh infection model. PLoS One. 2010;20(5):e10744. Epub 2010/05/28.
22 Mastoraki E, Michalopoulos A, Kriaras I, Mouchtouri E, Falagas M, Karatza D, *et al.* Incidence of postoperative infections in patients undergoing coronary artery bypass grafting surgery receiving antimicrobial prophylaxis with original and generic cefuroxime. J Infect. 2008;56(1):35–9.
23 Rodriguez CA, Agudelo M, Cataño JC, Zuluaga AF, Vesga O. Potential therapeutic failure of generic vancomycin in a liver transplant patient with MRSA peritonitis and bacteremia. J Infect. 2009;59(4):277–80.
24 Rodriguez CA, Agudelo M, Zuluaga AF, Vesga O. Generic vancomycin enriches resistant subpopulations of *Staphylococcus aureus* after exposure in a neutropenic mouse thigh infection model. Antimicrob Agents Chemother. 2012;56(1):243–7.
25 Concia E, Novelli A, Schito GC, Marchese A. Ideal microbiological and pharmacological characteristics of a quality antimicrobial agent: comparing original and generic molecules. J Chemother. 2007;19(6):609–19.
26 Richards G, Elliott E, Schaddock E. A comparison of the pharmacokinetics of aspen ceftriaxone and Rocephin in community-acquired meningitis. South African Med J. 2013;103(12):906–9.
27 US Food and Drug Administration FDA. FDA statement about product quality of parenteral vancomycin products, March 14, 2012. U.S. FDA, Rockville, MD. Available from URL: www.fda.gov/Drugs/DrugSafety/ucm295414.htm (last access 20 February 2014).
28 Kirkpatrick C, Ramzan R, Mykhaylo R, Mike B, Shahram G. Non-equivalence of antibiotic generic drugs and risk for intensive care patients. Pharmaceut Reg Affairs. 2013;2(1).
29 Baniasadi S, Dorudinia A, Mobarhan M, Karimi Gamishan M, Fahimi F. Microbial contamination of single- and multiple-dose vials after opening in a pulmonary teaching hospital. Braz J Infect Dis. 2013;17(1):69–73.
30 Centers for Disease Control and Prevention CDC. Invasive *Staphylococcus aureus* infections associated with pain injections and reuse of single-dose vials-Arizona and Delaware, 2012. MMWR Morb Mortal Wkly Rep. 2012;61(27):501–4.
31 Grohskopf LA, Roth VR, Feikin DR, Arduino MJ, Carson LA, Tokars JI, *et al.* Serratia liquefaciens bloodstream infections from contamination of epoetin alfa at a hemodialysis center. N Engl J Med. 2001;344(20):1491–7.
32 Manchikanti L, Falco F, Benyamin R, Caraway D, Wargo B, *et al.* Assessment of infection control practices for interventional techniques: a best evidence synthesis of safe injection practices and use of single-dose medication vials. Pain Physician. 2012;15(5):E573–614.