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Comparative Evaluation of Cephalosporin Injectable Product Manufactured by Generic and Innovator Company

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ABSTRACT

The main purpose of the study was to compare few physical parameters of the marketed products of Ceftriaxone Sodium for injection 1g manufactured by generic and innovator company nearing the expiry date. The marketed samples of generic and innovator company were tested for physical parameters like Appearance, pH, clarity, reconstitution time and primary packing quality. All the samples were reconstituted and pH was determined using calibrated pH meter. From the results it was found that few physical parameters were comparable in innovator and generic samples with respect to parameters like pH and clarity whereas phenomenal difference was observed in reconstitution time and appearance of the product. Innovator product showed very less reconstitution time, good clarity of reconstituted solution and acceptable physical appearance or description. The increase in reconstitution time & inferior physical appearance observations of generic product may be because of sourcing of raw materials from less regulated countries (economic source) or depends on other important processing parameters like method of manufacturing (different process employed by innovator and generic company), in-process controls, quality of starting materials or even quality of intermediates used for manufacturing of raw materials that is being sourced by the generic company.

KEYWORDS

Ceftriaxone sodium, Reconstitution time, Clarity and Appearance of the product.

INTRODUCTION

Ceftriaxone Sodium is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Chemically, Ceftriaxone sodium is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8- oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 72-(*Z*)-(*O*-methyloxime), disodium salt, sesquaterhydrate[1].

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Ceftriaxone Sodium (Figure 1)[1] is used to treat infections such as bacterial septicemia, meningitis, urinary tract infections, lower respiratory tract infections, acute bacterial otitis media, skin & skin structure infections, uncomplicated gonorrhea, bone & joint infections and pelvic inflammatory disease [1].

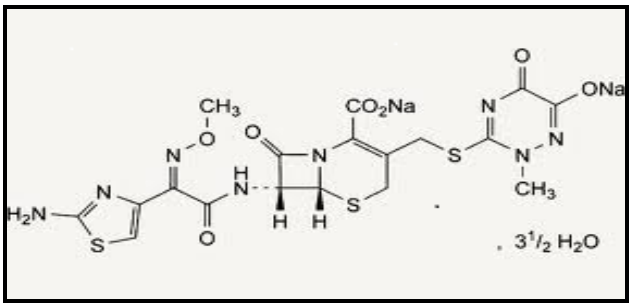

Figure 1: Chemical Structure of Ceftriaxone Sodium

Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of Ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity[1].

From the manufacturer's guidelines, Ceftriaxone sodium is stable at room temperature for 24 hours to 10 days when the drug is reconstituted in specified diluent as recommended by innovator company or the generic manufacturer, provided the reconstituted solution is stored as per storage requirements given on patient information leaflet (PIL) [1].

The stability of Ceftriaxone sodium reconstituted in solution is influenced by the following factors: [1]

a. **Storage Temperature:** The drug is stable for longer time in solutions stored at 4°C than in solutions stored at temperature not exceeding 25°C.

b. **Type of Fluid for Reconstitution:** The drug is reconstituted in various diluents and is stable for a period ranging from few hours to 10 days provided the reconstituted solution is stored as directed in PIL of innovator or generic manufacturer.

Most of the raw material for manufacture of Ceftriaxone sodium injection is imported from less regulated countries since they are cost effective. The raw material is imported only when the manufacturing company follows current Good Manufacturing Practice standards set by the federal agencies. From India, DCGI (Drug Controller General of India) inspects the facility of the importer periodically before giving approval to a pharmaceutical manufacturing facility and then approves for the import of the raw material.

Ceftriaxone sodium for injection has to be reconstituted just before use with sterile water for injection or suitable diluents recommended by the manufacturer as given in PIL. Complete reconstitution within short period of time is very important whereas incomplete reconstitution of the product indicates the stability issue of the product which will have direct implications on patient's health and safety. The stability of the product can be assessed by evaluating various parameters like Reconstitution time (In House test), pH of the reconstituted solution, clarity, discoloration of product, water content etc.

The objective of present study was comparative evaluation of various physical parameters like Appearance, pH, Clarity, Reconstitution time and quality of primary packing between generic and innovator products of Ceftriaxone sodium for injection of 1g strength. This comparison is done before the expiry date of the product (i.e.,products nearing expiry date) to find out the efficiency and quality of product till the end of the shelf life. For this study, near expiry samples were randomly procured from retail pharmacy outlets.

MATERIALS AND METHODS

Materials

a. Generic & Innovator Finished Product: Five formulations of Ceftriaxone sodium for injection marketed by generic and innovator company were randomly procured from retail pharmacy.

b. Other Requirements: Calibrated pH meter (EUTECH pH 510), magnifying lens, black and white background, syringes, 10 mL sterile water for injection, standard buffer solutions, virgin white paper for inspection, Proper illumination for inspection and calibrated stopwatch.

Methods

Method of Reconstitution

Reconstitution was carried out using 10 mL of sterile water for injection for 1 g Ceftriaxone sodium injection[1]. Before reconstitution, vial has to be checked with respect to flip off seal integrity and any other observations. After removing the flip off, 10 mL of water for

injection was injected into the vial through the rubber stopper using a sterile syringe. The vial was then shaken vigorously until all the powder had dissolved and no particles were present. The criteria used to attain consistent end point to define full reconstitution was no apparent particulate matter and clear solution [2]. The time taken for complete reconstitution was noted and this test was performed randomly using 5 generic and 5 innovator samples.

Determination of pH

The pH of reconstituted solution was determined potentiometrically by means of a glass electrode and a reference electrode using a pH meter. The pH meter was calibrated using standard buffer solutions before measuring the pH of reconstituted solutions.

Determination of Clarity

Samples were reconstituted as per the directions stated on the label or pack insert leaflet. Clarity of reconstituted solutions was observed against a visual inspection board with a black and white background under sufficient illumination. Presence of black particles can be seen using white background whereas any white particles and fibers present can be observed against black background.

Determination of Product Appearance & Quality of Primary Packing

Product appearance was checked visually using a clean white surface (Tile) and a magnified lens. Primary packing quality was checked visually for labeling quality, flip off sealing quality etc.

RESULTS AND DISCUSSION

The United States Pharmacopoeia (USP) 2006, defines completeness of reconstitution as the state where the solid dissolves completely, leaving no visible residue as undissolved matter or the constituted solution is not significantly less clear than an equal volume of the diluent or purified water present in a similar vessel and examined under similar conditions[3].

Reconstitution time of both Innovator and Generic product is depicted in Table 1 and graphically shown in Figure 2 respectively. Innovator product dissolved very quickly in sterile water for injection showing a reconstitution time of about 25 seconds. Reconstitution time of the generic product was about 120 seconds. This comparison of reconstitution time between innovator and generic product can be clearly understood with the help of graphical representation in Figure 2.

According to the Indian Pharmacopoeia (I.P) 2007, the pH range of reconstituted solution of Ceftriaxone sodium for injection should be in the range of 6.0 – 8.0 [4]. If the pH is out of this range it indicates the changes in chemical properties of the drug or any other degradation or contamination which is threat to the patient. The pH values of both generic and innovator products are comparable and all the values are within the range as prescribed in I.P. The data is shown in Table 1 and graphically depicted in Figure 3 respectively.

Table 1: Reconstitution time & pH of Innovator and Generic product

Vial No.	Reconstitution time (seconds)		pH of Reconstituted solutions	
	Innovator Product	Generic product	Innovator Product	Generic Product
1	15	120	6.54	6.60
2	18	120	6.56	6.51
3	19	120	6.55	7.12
4	12	120	6.59	7.04
5	25	120	6.57	6.98

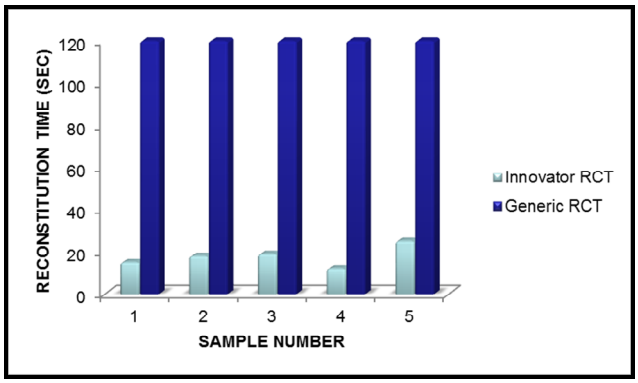

Figure: 2 Comparison of Reconstitution time of Innovator and Generic product

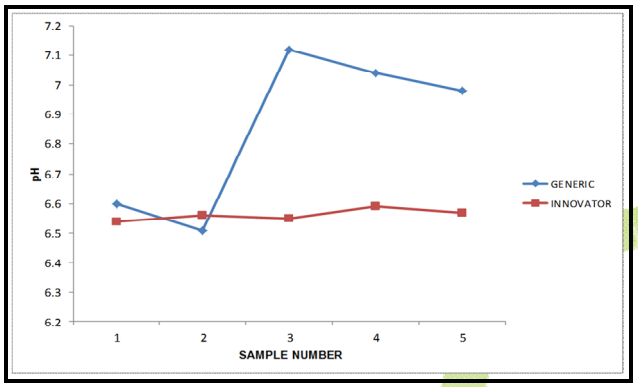

Figure: 3. Comparison of pH of Innovator and Generic product

Ceftriaxone powder for injection exists in the form of white to yellowish orange crystalline powder. This crystalline form of the drug affects properties like aqueous solubility, reconstitution time and chemical stability. The color of the product mainly indicates chemical stability. According to I.P, the product should be white to yellowish orange crystalline powder till the shelf life[4]. Innovator product is off white crystalline powder whereas generic product is yellow crystalline in color (Table 2). The color development of the reconstituted solution indicates formation of degradation products and it affects the stability of product after reconstitution (Table 2). The reconstituted solutions are pale yellowish in color and the color of the generic product reconstituted solution is more yellowish when compared to innovator product. This observation was more prominent in generic product than in innovator product.

Table 2: Appearance of dry powder for injection & Color of reconstituted solutions of Innovator and Generic product (*Reported only for information purpose)

Vial No.	Appearance of the product		Color of reconstituted solution*	
	Innovator Product	Generic product	Innovator product	Generic product
1	Off white powder	Yellow powder	Pale yellow	Dark yellow
2	Off white powder	Yellow powder	Pale yellow	Dark yellow
3	Off white powder	Yellow powder	Pale yellow	Dark yellow
4	Off white powder	Yellow powder	Pale yellow	Dark yellow
5	Off white powder	Yellow powder	Pale yellow	Dark yellow

Clarity of the reconstituted solution is determined to observe whether the solid had dissolved completely without leaving any visible residue in solution. It also helps to determine the presence of any foreign particles or other contaminants like fibers and charred black particles. Innovator product is very clear when compared to generic product however both innovator and generic product did not contain any foreign particles or contaminants.

Packaging quality of finished product is determined by visual inspection. USP specifies that “containers, including the closures for dry powder solids intended for parenteral use, do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale and use.” The packaging quality differences seen between Innovator and Generic product are

Table.3. Comparison of primary packing quality of Innovator and Generic Product

S. No.	Innovator product	Generic product
1	Uniform spreading of label is found and adhesion of label quality is good	Wrinkles and uneven adhesion of label is observed
2	Quality of batch coding on the label is acceptable and good	Smudging of print with respect to batch over coding detail is observed
3	Ceftriaxone sodium powder is not adhered to the inner side walls of the vial and the powder is free flowing	Ceftriaxone sodium powder is adhered to the inner side walls of the vial and the powder is not free flowing

shown in Table 3. From the table it is clear that overall packaging quality of innovator product is very good when compared to generic product.

CONCLUSION

From the results, it is evident that phenomenal difference between generic and innovator product is observed in terms of reconstitution time and appearance. Reconstitution time for generic product is very high when compared to innovator product. This implies that generic product nearing expiry date is not efficient and user friendly as that of innovator product nearing expiry date. The difference may be because of variations in the physico-chemical properties of input raw material obtained by the generic company which is usually imported from less regulated markets as they are cost effective & economic and also may be because of different manufacturing process employed by innovator and generic company. Finally to conclude, establishing proper limits for input sterile raw material or intermediates will help in controlling the reconstitution time and product appearance of generic product throughout its shelf life.

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