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Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

RESEARCH ARTICLE

IN-VITRO BIOEQUIVALENCE STUDY FOR MARKETED INNOVATOR AND THREE BRANDS LOCAL MANUFACTURING CIPROFLOXACIN HYDROCHLORIDE TABLETS IN YEMEN

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Article Info:

Article History:
Received: 7 August 2023
Reviewed: 16 September 2023
Accepted: 23 October 2023
Published: 15 November 2023

Cite this article:
Alzomor AKY, Al-Madhagi WM, Aljbry M, Almontser S, Al-Absi S, Khalid M. *In-vitro* bioequivalence study for marketed innovator and three brands local manufacturing ciprofloxacin hydrochloride tablets in Yemen. Universal Journal of Pharmaceutical Research 2022; 7(5):12-17.
https://doi.org/10.22270/ujpr.v7i5.835

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Abstract

Background and objective: This study is focused to evaluate the *in vitro* bioequivalence of three brands of ciprofloxacin 500 mg tablets from local producer and marketing in Yemen, with innovator brand using *in vitro* dissolution study under biowaiver conditions by UV spectrophotometer.
Method: The Dissolution profile has been evaluated by testing in dissolution media were USP buffer solution at pH 1.2 (hydrochloric acid solution), pH 4.5 (acetate buffer solution) and pH 6.8 (phosphate buffer solution). Also, further general quality assessment tests of these tablets like weight variation, disintegration time hardness, friability and assay test were accomplished according to proven methods.
Results: All brands conformed to the official specification for uniformity of weight, friability and disintegration time. Content uniformity of chosen tablets shown that all samples contained over 99% (w/w) of labeled chemical content. The profile dissolution finding of all the tablets formulation and the innovator brand were further analyzed with difference factor (f_1) and similarity factor (f_2).
Conclusion: These results indicated that the generic Cipro® (C) tablets included in this study was bioequivalent with the chosen innovator brand at 0.2N hydrochloric acid solution, pH 1.2 and the other generic brands bioequivalent with the chosen innovator brand at this medium. Also, the results showed that the three generic ciprofloxacin tablets involved in this study were bioequivalent with the selected innovator brand at pH 4.5 and pH 6.8.
Keywords: Biowaiver, Ciprofloxacin tablet, Dissolution profile.

INTRODUCTION

The progression of dissolution has an important role in drug release from its dosage form and making it accessible for following gastrointestinal absorption. So, dissolution examination of pharmaceutical solid dosage form is a very vital test of product quality and it can be used as a curate method for distinguishing between formulations of the same active ingredient[1,2]. Drug dissolution is reliant on various factors, which include not only the physicochemical properties of the drug, but also the formulation of the dosage form and the manufacturing process[3]. Therefore, constant dissolution analyses of promoted drug brands are important to ensure availability of medicines quality.

Ciprofloxacin is derivative of synthetic fluoroquinolone with board range of activity. It is usually used in the treatment of soft tissue, lower respiratory tract infections, urinary tract infections, and skin infections, bacterial diarrhea, joint and bone infections, and in surgical prophylaxis[4]. Ciprofloxacin is considered to be the drug of choice to increase supply and also local manufacture of generic brands of ciprofloxacin in the market. It is general psychology that the quality of local manufacturing products is well-thought-out poor when equated to import generic and innovator products available in the market[5]. World Health Organization (WHO) has continuously maintained the use of generic drug products aiming to improve the overall health care system[6]. The generic substitution can be measured when a generic brand of an innovator drug holds identical quantities of the same active constituent in the same does, same dosage and route of administration along with required standards for purity, quality,

identity and strength[7]. The local manufacturing generic brands are frequently much cheaper than its innovator as generic manufacturers do not have similar venture costs for the development of a new drug. So as to substitute the innovator with generics while keeping therapeutic usefulness, dissolution testing can be used as a tool to distinguish between acceptable and unacceptable drug brands[8]. It can be used as assign for bioequivalence; dissolution testing is applied and economic method that can be followed when there are limitations for performing *in vivo* study[6].

In the current study, *in vitro* bioequivalence of three local manufacturing brand ciprofloxacin HCl tablets 500 mg were studied in comparison to an innovator brand of ciprofloxacin HCl tablet 500 mg to explain the quality of local manufacturing substitution of ciprofloxacin generic products in the Yemeni market.

Numerous reports on comparative dissolution study of ciprofloxacin tablets of various countries have been published[9] estimated six brands of ciprofloxacin 500 mg tablet available in Jos, Nigeria and found that only three brands 50% could be used interchangeably with their chosen, innovator brand six[10]. In a previous study six generic ciprofloxacin tablets were evaluated produced by various manufacturer in India and reported that all 100% generic ciprofloxacin tablets were bioequivalent with the selected innovator brand seven[11]. Kyriacos *et al.*, studied ten brands of ciprofloxacin tablet available in Lebanese market and found significant differences between some brands in terms of hardness, disintegration and dissolution eight[12]. This study is for ciprofloxacin brands available in Yemen. So, the present work was undertaken to assess the performance of our local products.

MATERIALS AND METHODS

Ciprofloxacin HCL, working standard (Denk Pharma, Germany) was kindly donated from Shifaco Pharmaceutical Company. Innovator brand (Cipro-IB) and three generic ciprofloxacin 500 mg tablet products (Cipro-A, Cipro-B and Cipro-C) were randomly selected and purchased from Community pharmacies in Sana'a, Yemen. The innovator and generic brands were taken from market that they have a minimum one year before expiry date. Reagents utilized including Hydrochloric acid, Ortho-phosphoric acid, Sodium acetate, Triethylamine, Acetonitrile, and analytical grade of Sodium hydroxide. (Scharlau, Spain).

Physicochemical Parameters

The dimensions (length and diameter) of the tested tablets and hardness were determined using tablet hardness tester (Length, hardness tester TBH 125, Erweka, Germany) by means of ten tablets form each of the studied brands, the average and standard deviation were determined for the studied innovator and the three generic products. Weight uniformity test was performing using twenty tablets form each of the studied brands, the average weight, the upper and lower limit and standard deviation were determined for the studied innovator and the three generic brands. Disintegration and friability tests for studied tablets were evaluated by disintegration tester (Disintegration tester model, Pharma Test, Germany) and tablet friability tester (Friability tester model, Pharma Test, Germany) respectively based on the pharmacopeia. Calibration curve for measuring the accuracy and precision of HPLC instrument was performed by preparing different concentration (0.02, 0.04, 0.06, 0.08 mg/ml) from ciprofloxacin HCl standard material and measuring it by HPLC at 278 nm. The measurement was repeated at different time and the average reading (AUC) were plotted vs concentration. Assay test for drug potency of the tested ciprofloxacin tablet products were performed by preparing the mobile phase as the ratio (13 ml of acetonitrile and 87 ml of a 0.245% w/v solutions of ortho-phosphoric acid and the pH of which has been adjusted to 3.0 with triethanolamine), then standard and the samples for each brand were prepared at the final concentration 0.05% according to the (USP. 2012) and measuring by HPLC (HPLC system, WATERS, USA) at wavelength 278nm.

Comparative dissolution profile

Ciprofloxacin tablets dissolution test was done based on USP ciprofloxacin tablet monograph dissolution method for innovator and the three generic brands. The Dissolution profile was done using dissolution tester (DT 600, Erweka, Germany) apparatus-II. Operated at 50 rpm. The evaluation was done using three different mediums according to WHO guidance suggested. The first dissolution medium is 900 ml 0.01N HCI (pH 1.2), kept at 37±0.5°C. Six tablets from each brand were withdrawn at 5, 15, 30 min, and the volumes taken, substituted with fresh dissolution medium, samples were then filtered, diluted and evaluated by spectrophotmetrically at 276nm (UV-Vis spectrophoto-meter, SP-3000 PLUS, Optima Tokyo, Japan). Also, the same process was performed using acetate medium 900 ml pH 4.5 and phosphate medium 900 ml pH 6.8.

Dissolution profile data analyses

Recommended FDA (United States Food and Drug Administration) Methods used for evaluation of dissolution to determine the immediate release solid dosage forms were used in this study[12]. A simple approach used difference factor (f_1) and a similarity factor (f_2) were determined to compare dissolution profiles among innovator and the three generic brands. The difference factor (f_1) calculates the percent (%) difference among the two curves at each time point and is a measurement of the relative error between the two curves[13].

$$f_1 = \{[\Sigma^{n}_{t=1} / R_t - T_t /] / [\Sigma^{n}_{t=1} R_t]\} * 100$$

Where (n) is the number of time interval points, (R_t) is the dissolution value of the innovator at time (t) and (T_t) is the dissolution value of the generic product under test at time (t). The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error, it is a measurement or the similarity in the percent (%) dissolution amongst the two curves[13].

$$F_2 = 50 * \text{Log} \{[1 + (1/n) \Sigma^{n}_{t=1} (R_t - T_t)^2]^{-0.5} * 100$$

Curves can be determined similar when (f_1) values are close to 0, and (f_2) close to 100. (f_1) values from (0-15) and (f_2) values from (50-100) certify similarity or bioequivalence of the two curves and the performance of the product under test with innovator product[14].

RESULTS

Physicochemical parameters and product label information

Product label information for the innovator and three generic ciprofloxacin brands are displayed in Table 1. Reviewing the manufacture date and expiry date for the marketed brands shows wide differences in Labeled expiry date time. The longest expiry date period was 3 years and it fit in to the innovator and all of the generic products. Variances in expiry date period could give an indication that utmost of the genetic products do not have the same stability accomplished by the innovator product. Dimensions, shape. Color and packaging description for the selected ciprofloxacin tablet brands are showed in Table 1.

Table 1: Physical properties for four brands of ciprofloxacin tablets.

Brand Name	Code	MF. D	Exp. D	Shape	Taste	Color
CIPRO-DENK 500 mg, 10 tab	IB	4/2018	3/2021	Oblong	Characters	White
CIPROXE 500 mg, 10 tab	A	9/2018	9/2021	Oblong	Characters	White
CIPOSAN 500 mg, 10 tab	B	3/2018	3/2021	Oblong	Characters	White
CIPROFAST 500 mg, 10 tab	C	2/2018	2/2021	Oblong	Characters	White

The studies brands have oblong shape and have close dimensions to the innovator. Color for all products under study was white color. Tablet color might have a positive or negative psychological effect on patients[15], the change of color without a reference could have a negative effect on patients. All tested ciprofloxacin tablets were scored. This kind of scoring is usually used to give half dose if needed. The packaging materials of the products under study are transparent packaging material.

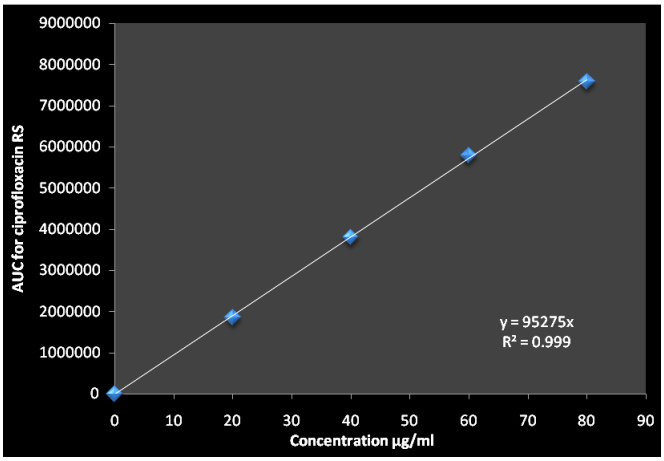

Figure 1: Calibration curve of Ciprofloxacin by HPLC.

Table 2: Physicochemical parameters of four brands of ciprofloxacin tablets 500 mg.

Test name/Brand Codes	weight variation (mg)	Hardness (Kg)	Friability (%)	Disintegration Time(min)	Assay (%)
Cipro-IB	733.9	14.4799	0.07%	1	99.25
Cipro-A	691.5	13.8477	0.18%	1	100.08
Cipro-B	760.03	15.2957	0.17%	2	99.57
Cipro-C	682.0	11.0153	0.05%	1	102.08

Calibration curve

Linearity was demonstrated by analyzing four different concentrations of ciprofloxacin working standard and the average of AUC were recorded for the different conc. Table 1. Calibration was constructed by plotting average of AUC vs concentrations Figure 1. From the Figure 1 below represent correlation coefficient (R^2)= 0.9997) not more than 1 and not less than 0.9, but R2 between linearity limit (0.9–1). This linearity indicates HPLC system which used for measuring different concentration of ciprofloxacin is calibrated and appraises. Weight variation, hardness, friability, disintegration, and assay percent of the tested brands are summarized in Table 2 Weights of generic brands were close to innovator product. Approximately 733.9 mg and all the brands also gave deviation from innovator weight. It gads around 51 mg lower weight and 27 mg higher weight than innovator.

Hardness, friability, and assay results for all tested brands were similar to the innovator. Disintegration time finding for all evaluated brands was similar to innovator giving nearly 1 min disintegration time of 2 min. This 2 fold increase in disintegration for brand Cipro-B could have a negative impact on dissolution finding for tablets and it could be credited to using different manufacturing technique like using wet granulation instead of direct compression, using different excipients.

Comparative dissolution profile test:

Result of dissolution profile test for four brands of ciprofloxacin 500 mg tablet at different pH 1.2, 4.5 and 6.8 are presented in Table 3.

Table 3: Results of % dissolution profile for four brands of ciprofloxacin 500 mg tablets at pH 1.2, 4.5 and 6.8.

	Cipro-IB	Cipro-A	Cipro-B	Cipro-C	Cipro-IB	Cipro-A	Cipro-B	Cipro-C	Cipro-IB	Cipro-A	Cipro-B	Cipro-C
	pH 1.2 (Hydrochloric acid solution)				pH 4.5 (Acetate buffer solution)				pH 6.8 (Phosphate buffer solution)			
5 min	78.7	51.12	59.9	80.77	88.66	63.22	72.16	97.13	0.3	1.03	0.136	23.5
15 min	92.45	90.06	91.99	91.003	90.12	100.34	102.19	105.14	5.49	6.87	4.8	33.79
30 min	97.59	99.25	98.96	101.74	95.53	100.8	102.8	115	5.32	8.14	6.15	37.12

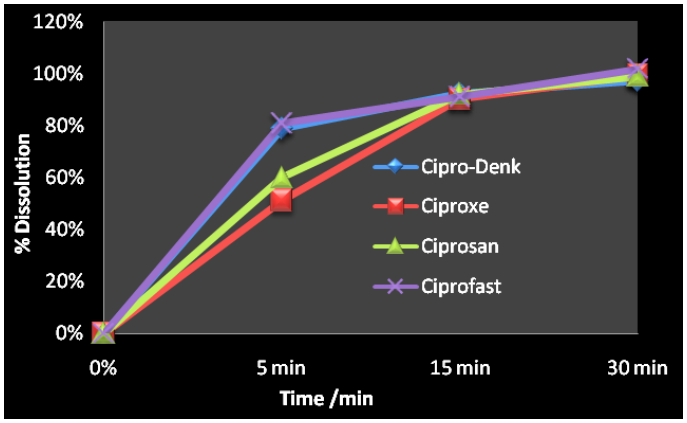

Figure 2: Dissolution profiles of all and the innovative brand ciprofloxacin 500 mg tablets in pH 1.2 (Hydrochloric acid solution).

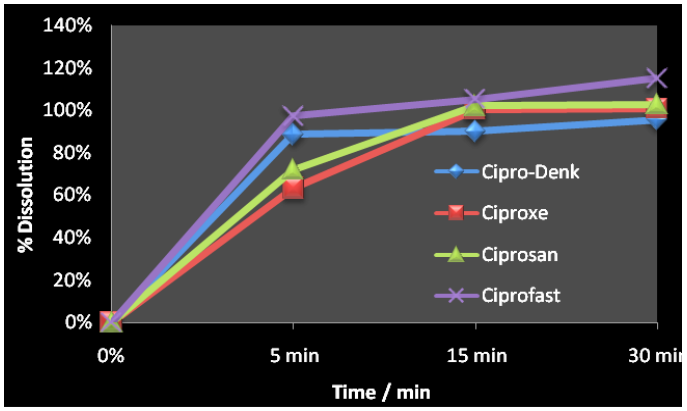

Figure 3: Dissolution profiles of all and the innovative brand ciprofloxacin 500 mg tablets in pH 4.5 (Acetate buffer solution).

DISCUSSION

All tested ciprofloxacin tablets brands observed with the compendial conditions for identity, weight uniformity, disintegration and assay, as well as the non-compendial test for hardness. The test for identity is essential to confirm that the brand contains the requisite API. The *t*R of ciprofloxacin HCl in all the samples was 2-2.2 min and closely corresponded to the *t*R of the ciprofloxacin HCl reference standard (2.02 min). The test for weight uniformity aids as a pointer to good manufacturing practice and to guarantee that the drug content in every unit dose is dispersed within a narrow range around the label strength[16]. Hardness is a non-official test that evaluates the ability of tablets to endure handling during packaging, transportation and usage without splitting or chipping. It can also affect further parameters such as friability and disintegration[17]. The harder a tablet, the less friable and the more time it takes to disintegrate. A force of about 4 Kg is the minimum condition for a suitable tablet[18]. Brand Ciprofast essential the least quantity of pressure (11.02 Kg) to break as summarized in Table 3. The disintegration test measures the time required for a tablet to disintegrate into particles when in contact with gastrointestinal fluids, and different formulation factors are identified to affect it.

There was a wide inter-brand variation in the disintegration time. Nevertheless, all evaluated brands conformed with pharmacopoeia specification which stipulates a disintegration time of not more than 30 min for film coated tablets[15]. There was no direct association between tablet hardness and disintegration time. The goal of the assay specification is to guarantee the presence of the API in requisite amount significant variation in the amount of API could lead to ineffective therapeutic drug levels or overdosing that may cause toxicity[19]. Compendial specification requires that ciprofloxacin tablets must contain not less than 90.0% and not more than 110.0% of the stated amount[12]. The highest percentage content was obtained for brand Cipro-denk (99.25%). Dissolution profile of the innovator and three locale generic brands at acidic medium pH 1.2 are summarized in Figure 3.

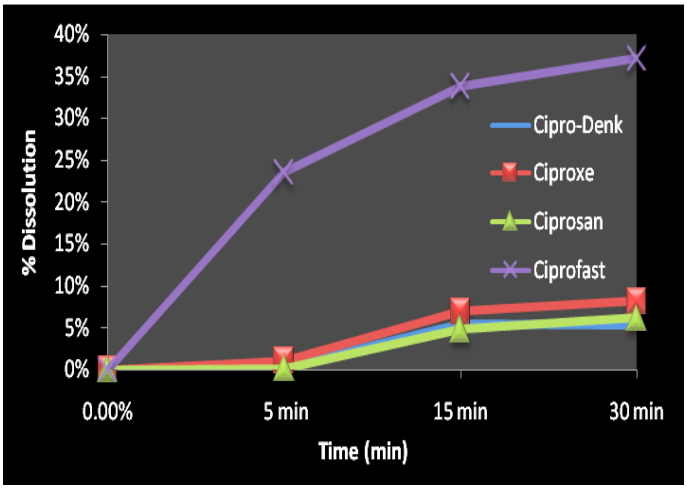

Figure 4: Dissolution profiles of all and the innovative brand ciprofloxacin 500 mg tablets in pH 6.8 (Phosphate buffer solution).

Generic products (Ciprofast) appear to be very close to innovator (Cipro-denk) in results in all time intervals. The most noticeable difference in dissolution is recorded at the 5 min time interval, where (ciproxe) generic products displayed approximately 26% lower release than innovator, drug release 51.12% on average (Ciprosan) generic products exhibited 18% lower drug release than innovator, drug 59.9% on average at pH 4.5 most of the generic brands released more that 85% of ciprofloxacin HCI within 30 min. Nevertheless, all the products including the innovator brand Cipro® had very poor release characteristic at pH 6.8. This remark is reliable with the solubility of ciprofloxacin that displays a "U" shaped pH – solubility profile with high solubility at pH values below 5 and above 10, and low solubility close the isoelectric point (pH 7)[20].

Table 4: The difference factor (f1) and similarity factor (f2) for all generic ciprofloxacin tablets brand in respect to Innovator (Cipro-IB).

Products	pH 1.2		pH 4.5		pH 6.8	
	F2	F1	F2	F1	F2	F1
Cipro-A	40	12	40	15	84	44
Cipro-B	48	8	45	13	96	15
Cipro-C	77	3	41	16	28	75

Dissolution profile data Analysis ciprofloxacin HCI is classified based on BCS (biopharmaceutical classification) as class III group of drugs**.** The minimum condition for accepting ciprofloxacin instant release tablet dosage forms are stated by USP ciprofloxacin monograph. It conditions that the amount of not less than 85% (Q) of the labeled amount of ciprofloxacin dissolved in 30 min**.** All studied products passed this dissolution test limit at acidic medium pH. 1.2 and at acetate butted pH 4.5 but not accepted at phosphate buffer pH 6.8. Ciprofloxacin is highly soluble at pH 1.2 and 4.5. So, higher dissolution was found in these two media. Ciprofloxacin has limited solubility at pH 6.8 (<0.02 mg/ml) so, 37.17% dissolution is acceptable in case of phosphate buffer medium (pH 6.8)**.** According to the FDA guidance for industry, in the dissolution testing of immediate release solid oral dosage forms, the BCS recommends that for class I and in some cases class III drugs 85% dissolution in 0.1 N in HCL in 15 min confirms that the bioavailability comply with requirement of monograph[13]. The innovator (Ciproxe) and (Ciprosan) are accepted the stated limit after 15 min of dissolution as the average drug dissolution was higher than 15 min of dissolution profiles of the tested innovator and brand products, a model independent approach of difference factor (f1) and similarity factor (f2) were working[14]. Similarity factor f2 has been done by FDA and the European medicines evaluation agency (EMEA) to compare the similarity of two or more dissolution profiles. For two dissolution profiles to be measured bioequivalent or similar, difference factor (f1) should be between 0 and 15, while similarity factor (f2) should be between 50 and 100[14]. The difference factor (f1) and similarity factor (f2) values for the different generic products under Study with respect to innovator (Cipro-Denk) are summarized in Table 4 at different pH. At pH 1.2 the calculated values of similarity factor (f2) more than 50 and difference factor (f1) values were less than 15 for were evaluated product (Ciprofast) can be measured to be equivalent to the innovator brand. (Ciproxe and Ciprosan) generic products had a (f2) value of 40 and 48 less than 50 and (f1) value of 12 and 8 less than 15

Since the value (f1) factor is within the limit (0-15) and the (f2) factor is lower than 50, (Ciproxe and Ciprosan) are measured to be dissimilar and not bioequivalent to innovator. At pH 4.5 the considered values of similarity factor (f2) were less than 50 for all the three generic brand (Ciproxe, Ciprofast and Ciprofast) and difference factor (f1) values were within the limit (0-15) for studied products (Ciproxe and Ciprosan) and generic product Ciprofast is more than 15. So, all the three generic products are measured to be dissimilar and not bioequivalent to innovator. Similar study done in Nigeria, where three (50%) of the six tested ciprofloxacin tablets brands were estimated pharmaceutically nonequivalent to the innovator Cipro brand**.**

CONCLUSIONS

At pH 6.8, the amount of ciprofloxacin HCl done for all the generic brands and the Innovator brand (IB) was less than 85% within 30 min. So, the difference factor f1 and similarity factor f2 are not appropriate for the dissolution data found factor at pH 6.8 due to low drug release. The low drug release at pH 6.8 even for the IB is predictable assumed the pH- dependent solubility of ciprofloxacin that is lowest at neutral pH.

ACKNOWLEDGEMENTS

The authors express their gratitude to Pharmaceutics Laboratoires in Al-Nasser University, and Global Pharma Company, Sanaa, Yemen; for supplying all Materials and Equipment That use in This research.

AUTHOR'S CONTRIBUTION

Alzomor AKY: study design, follow up the experimental part. **Al-Madhagi WM:** writing up and analyzing data. **Aljbry M:** experimental work. **Almontser S:** editing, methodology. **Al-Absi S:** formal analysis, conceptualization. **Khalid M:** research design, data collection. All the authors approved the finished version of the manuscript.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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