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Review Article

Aripiprazole and Clozapine: A Review of Spectroscopic and Chromatographic Method

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ABSTRACT

Aripiprazole and Clozapine are classified as an Atypical Antipsychotics. Aripiprazole primarily used in the treatment of schizophrenia and bipolar disorder. Clozapine works by changing the actions of chemicals in the brain. It is used to treat severe schizophrenia, or to reduce the risk of suicidal behavior in people with schizophrenia or similar disorders. It is also used in Parkinson's disease. The clinical and pharmaceutical analysis of these drugs requires effective analytical procedures for quality control and pharmacodyna44mic and pharmacokinetic studies as well as stability study. There are many analytical methods reported so far in the literature for the determination of Aripiprazole and Clozapine in Biological samples and pharmaceutical formulations. This article comprises reviews of analytical methods like Spectrophotometric methods, chromatographic methods.

Key-words: Aripiprazole, Clozapine, Spectrophotometry, HPLC

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INTRODUCTION:

ARIPIPRAZOLE:

Aripiprazole is an Atypical Antipsychotic drug. It is primarily used in the treatment of schizophrenia and bipolar disorder. Although it is used as an add-on treatment in major depressive disorder, tic disorders, and irritability associated with autism. Aripiprazole have partial agonistic activity at D2 receptor, also have partial agonist activity at 5-HT1A receptor, and have antagonist activity at 5-HT2A receptor.

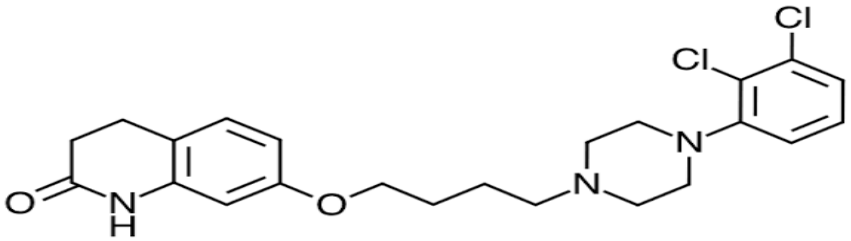

Figure 1: Structure of Aripiprazole

Table 1: Structural identification of Aripiprazole

Sr. no.	Class	Identification
1	Kingdom	Organic compound
2	Super Class	Organohetrocyclic compound
3	Class	Diazinanes
4	Sub class	Piperazines
5	Direct parent	Phenylpiperazines
6	Alternative parent	N-arylpiperazines, Hydroquinolones, Substituted anilines, Dichlorobenzens, Dialkylarylamines, N-alkylpiperazines, Alkyl aryl ethers, Aryl chlorides, Trialkyl amines, Secondary carboxylic acid amides, Azacyclic compounds, Organochlorides, Hydrocarbon derivatives, Carbonyl compounds
7	Molecular framework	Aromatic heterocyclic compound

Table 2: Drug Profile

Sr. No.	Parameters	Description
1	Category	Antipsychotic agent
2	Chemical Formula	$C_{23}H_{27}Cl_2N_3O_2$
3	IUPAC Name	7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxyl}-1,2,3,4-tetrahydroquinolin-2-one
4	Molecular Weight	448.38538 g/mol
5	Characteristic	Colorless, flake crystals from ethanol
6	Solubility	Soluble in Methanol, Ethanol and slightly soluble in water

Table 3: OFFICIAL METHODS FOR ESTIMATION OF ARIPIPRAZOLE

Aripiprazole is official in Indian pharmacopoeia (IP 2014) and United State Pharmacopoeia (USP 2012).

Sr. No.	Drug	Method	Description	Ref. No.
1	Aripiprazole (IP 2014)	**Liquid Chromatography**	**Detection Wavelength:** 220 nm **Mobile Phase:** Potassium Dihydrogen orthophosphate: Triethylamine (pH 3): methanol: Acetonitrile (50:2:25:25 v/v/v/v) **Stationary Phase:** Stainless Steel Column 25 cm × 4.6 mm, packed with Octadecylsilane bonded to porous silica (5µm). **Flow Rate:** 1 ml/min	7

			Injection Volume: 20 µl	
2	Aripiprazole Tablet (USP 2012)	**Liquid Chromatography**	**Detection Wavelength:** 254 nm **Solution A:** 2.8 g/L of anhydrous sodium sulfate in water **Mobile Phase:** Acetonitrile: Methanol: Sloution A: Glacial Acetic Acid (33:11:56:1) **Stationary Phase:** Octylsilane Boned to totally porous microsilica particles, 3 to 10 µm in diameter, 4.6 mm×15 cm **Flow Rate:**1 ml/min **Injection Volume:** 20 µl	8

TABLE 4: REPORTED METHOD OF ARIPIPRAZOLE

Sr No.	Drug	Method	Description	Ref. No.
1	Aripiprazole in Bulk and Pharmaceutical formulation	**UV Spectroscopy**	**Detection Wavelength:** 219 nm **Solvent:** Methanol **Linearity Range:** 2-10 µg/ml **Correlation coefficient:** 0.9998	9
2	Aripiprazole in tablet dosage forms	**Visible Spectrophotometric Method**	**Detection Wavelength:**414 nm **Solvent:** HCl **Linearity Range:**10-60 µg/ml **Coloring Agent:** Bromocresol green dye **Correlation coefficient:** 0.9968	10
3	Aripiprazole in tablet dosage forms	**UV Spectrometry**	**Detection Wavelength:** 218 nm **Solvent:** 0.05 M Phosphoric Acid: Acetonitrile (40:60 v/v) **Linearity Range:** 2.5-20 µg/ml **Correlation coefficient:** 0.9992 **LOD:** 0.01µg/ml **LOQ:** 0.1 µg/ml	11
4	Aripiprazole in tablet dosage form	**UV Spectrophotometer** **A) Ion pair complex**	**Detection wavelength:** 514 nm **Solvent:** dilute sulphuric acid **Linearity range:** 4-26 µg/ml **Coloring Agent:** Erichrome Black T (EBT) **Correlation coefficient:** 0.9999 **LOD:** 0.9523 µg/ml **LOQ:** 3.1714 µg/ml	12
5	Aripiprazole in Tablet Dosage form	**RP-HPLC Method**	**Detection wavelength:**254 nm **Mobile Phase:** Acetonitrile:Sodium acetate buffer (55:45 v/v) **Stationary Phase:** Phenomenex Luna C18 column (250 mm length, 4.6 mm internal diameter, 5 mm particle size) **Flow Rate:**1 ml/min **Linearity Range:**2-12 µg/ml **Retention Time:** 6.84 min **Regression Coefficient:** 0.9995	13
6	Aripiprazole in	**UV**	**Detection Wavelength:** 256 nm	14

	Pharmaceutical Dosage Form	**Spectrophotometry**	**Solvent:** 95% ethanol **Linearity range:**5-30 µg/ml **Correlational Coefficient:**0.9995	
7	Aripiprazole in Tablet Dosage form	**Stability indicating liquid chromatographic column**	**Detection wavelength:** 254 nm **Mobile Phase:** Ammonium acetate buffer: Acetonitile: Methanol (50:40:10 v/v) **StationaryPhase:** Zorbax 150mm×4.6mm, C18 column with 5µm particles **Flow Rate:**1.5 ml/min **Linearity Range:**100-800 µg/ml **Regression Coefficient:** 1	15
8	Aripiprazole in Bulk and in pharmaceutical formulation	**RP-HPLC Method**	**Detection wavelength:**255 nm **Mobile Phase:** buffer: acetonitilre: THF (30:60:10) **Stationary Phase:** waters spherisorb 5µ ODS (24.6mm×250mm) column **Flow Rate:**1.5 ml/min **Linearity range:**1-100 µg/ml **Correlation coefficient:**0.999	16
9	Aripiprazole in Bulk and in pharmaceutical formulation	**RP-HPLC Method**	**Detection wavelength:** 283 nm **Mobile Phase:** 0.02 M Sodium Dihydrogen Orthophosphate: Methanol (30:70 v/v) **Stationary phase:** INTERSIL C18 column (250×4.6 mm I.D., particle size 5 µm) **Flow Rate:**0.8 ml/min **Linearity range:**48-145 µg/ml **Correlation Coefficient:**0.99988 **LOD:** 0.22 µg/ml **LOQ:** 0.66 µg/ml	17
10	Aripiprazole in Human Serum	**LCMS/MS**	**Stationary Phase:** API 3200 Triple quadrapole mass spectrometer using Chromolith, RP-18e column **Mobile Phase:** 5 m M Ammonium Acetate in Water: Acetonitrile (25:75 %v/v) **Linearity range:** 1-200 ng/ml	18
11	Aripiprazole in Bulk and its Pharmaceutical formulation	**RP-HPLC Method**	**Detection Wavelength:** 254 nm **Stationary Phase:** HSF5 C18 (4.6 mm × 250mm, 5µm) column **Mobile Phase:** Methanol: Acetonitrile: sodium sulphate buffer (25:50:50) **Linearity range:** 20-200 µg/ml **Flow rate:** 1.2 ml/min **Internal standard:** Caffiene	19
12	Aripiprazole in	**UV Spectroscopy**	**A) Charge-transfer:**	20

	Tablet dosage Form	**a) Charge Transfer** **b) Ion-Pair complexation**	**Π acceptor:** 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) **σ acceptor:** iodine (I_2) **Solvent & Detection Wavelength:** 457 nm in acetonitrile 364 nm in 1,2-dichloroethane **Correlation coefficient:** DDQ: 0.9997 I_2: 0.9998 **Linearity range:** DDQ: 10-120 µg/ml I_2: 2-28 µg/ml **LOD:** DDQ: 2.44 I_2: 0.39 **LOQ:** DDQ: 8.12 I_2: 1.31 **B) Ion-pair complexation:** **Coloring Agent:** Bromocresol green (BCG), Bromocresol purple (BCP) **Solvent:** 1,2-dichloroethane **Detection Wavelength:** BCG: 413 µg/ml BCP: 400 µg/ml **Correlation coefficient:** BCG:0.9997 µg/ml BCP: 0.9999 µg/ml **Linearity range:** BCG: 2-24 µg/ml BCP: 2-20 µg/ml **LOD:** BCG: 0.50 µg/ml BCP: 0.30 µg/ml **LOQ:** BCG: 1.68 µg/ml BCP: 1 µg/ml	
13	Aripiprazole in pharmaceutical formulations	**UV-VIS Sprctrometry**	**Detection Wavelength:** 480 nm **Solvent:** Chloroform **Linearity range:** 2-12 µg/ml **Coloring Agent:** 3-Methyl-2-benzothiazolinone-hydrazone (MBTH), Ferric chloride **Correlation coefficient:** 0.9999	21
14	Aripiprazole in human plasma	**SPE-UPLC-MS/MS**	**Mobile phase:** Methanol: 10mM ammonium formate (85:15 v/v) **Stationary phase:** UPLC BEH C18 (50 mm×2.1 mm, 1.7 µm) column **Internal Standard:** aripiprazole-d8 **Linearity range:** 0.05-80 ng/ml	22

15	Aripiprazole in pharmaceuticals and human plasma	**Chemiluminescence Method**	**Chemiluminance** of tris(1,10-phenanthroline)-ruthenium(II),$Ru(phen)_3^{2+}$ **Linearity range:** 1.8-18 ng/ml **Correlation coefficient:** 0.9951 **LOD:** 0.9 ng/ml	23
16	Aripiprazole in bulk	**Stability indicating Spectrophotometric and TLC-Densitometric Method**	**A) Spectroscopic Method** **Solvent:** Acetonirile **Detection Wavelength:** 217.2 nm, 229 nm **Linearity range:** 1-6 µg/ml **B) TLC-Densitometric Method:** **Standard solution:** 0.1 mg/ml **Detection Wavelength:** 255 nm **Mobile Phase:** Ethyl acetate: Methanol (11:4 v/v) **Stationary Phase:** TLC-Plate, 4 mm band length, 3 mm×0.45 mm slit dimention **Scanning Speed:** 20 mm/s	24
17	Aripiprazole in Human Plasma	**LC-ESI-MS Method**	**Internal Standard:** Zolpidem tartrate **Stationary phase:** Grace Smart RP 184.6×100 mm, 3 µ column **Mobile phase:** Methanol: Ammonium acetate buffer (95:5 v/v) **Linearity range:** 0.2-60 ng/ml **Flow Rate:** 0.6 ml/min **M/Z:** Aripiprazole: 448.03→285.14 Zolpidem tartrate: 308.13→235.25	25
18	Aripiprazole and dehydoaripiprazole	**Capillary-Electrophoresis**	**Detection Wavelength:** 214 nm **Solvent:** DMSO, Methanol **Capillary:** 60 cm length, 75 µm internal diameter **Running Buffer:** 2.5-20% MeOH-phosphate buffer, 1-10% DMSO-phosphate buffer, MeOH-DMSO-phosphate buffer **Linearity range:** 2-10 ng/ml	26
19	Aripiprazole and deydroaripiprazole	**HPLC-UV Method**	**Detection Wavelength:** 254 nm **Mobile phase:** Chloroform: n-heptane (3:7 v/v) **Stationary phase:** C18 STRODS-2, 5 µm **Internal Standard:** 7-[5-[4-(3-chloro-2-methylpheny)-1-piprazinyl]pentyloxy]-3,4-dihydro-	27

			2(1H)-quinolinone (OPC-14558) **Linearity range:** Aripiprazole: 2-600 ng/ml Dehydroaripiprazole: 2-160 ng/ml	
20	Aripiprazole and escitalopram Oxalate	**UV Spectrometry**	**Detection Wavelength:** Aripiprazole- 255 nm Escitalopram Oxalate- 238 nm **Solvent:** Methanol **Linearity Range:** Aripiprazole: 5-25 µg/ml Escitalopram Oxalate: 15-75 µg/ml **Correlation coefficient:** Aripiprazole: 0.999 Escitalopram:0.999 **LOD:** Aripiprazole: 0.129 µg/ml Escitalopram Oxalate: 0.223 µg/ml **LOQ:** Aripiprazole: 0.392 µg/ml Escitalopram Oxalate: 0.677 µg/ml	28
21	Aripiprazole and divalproex sodium in combined dosage form.	**RP-HPLC Method**	**Detection wavelength:** 210 nm **Mobile Phase:** Acetonitrile:0.32% KH2PO4 (60:40 v/v) **Stationary Phase:** C18 column (250×4.6 mm) in isocratic mode **Flow Rate:** 1 ml/min	29
22	Aripiprazole (ARP) and Tapentadol (TAP)	**UV-VIS. Spectrophotometry**	**Detection Wavelength:** 543 nm **Solvent:** Chloroform **Coloring Agent:** Chloranilic acid **Linearity range:** ARP: 80-400 µg/ml TAP: 200-1000 µg/ml **Correlation Coefficient:** 0.9999 **LOD:** ARP: 5.17 TAP: 82.5 **LOQ:** ARP: 15.66 TAP: 250	30

CLOZAPINE:

Clozapine is an Atypical Antipsychotic drug. It works by changing the actions of chemicals in the brain. It is used to treat severe schizophrenia, or to reduce the risk of suicidal behavior in people with schizophrenia or similar disorders. It is also used in Parkinson's disease.

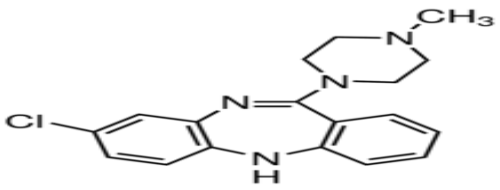

Figure 1: Structure of Clozapine

Table 5: Structural identification of Clozapine

Sr. no.	Class	Identification
1	Kingdom	Organic compound
2	Super Class	Organohetrocyclic compound
3	Class	Benzodiazepines
4	Sub class	Diabenzodiazepines
5	Direct parent	Diabenzodiazepines
6	Alternative parent	1,4-benzodiazepines, N-methylpiperazines, Cholorobenzines, Imidolactams, Aryl chlorides, Trialkylamines, Secondary amines, Propargyl-type 1,3-dipolar organic compounds, carboxamidines, Azacyclic compounds, Organochlorides, Hydrocarbon derivatives
7	Molecular framework	Aromatic heterocyclic compound

Table 6: Drug Profile

Sr. No.	Parameters	Description
1	Category	Antipsychotic agent
2	Chemical Formula	$C_{18}H_{19}ClN_4$
3	IUPAC Name	8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine
4	Molecular Weight	326.823 g/mol
5	Characteristic	Yellow Crystal
6	Solubility	0.1889 mg/ml in water

TABLE 7: OFFICIAL METHOD ESTIMATION OF CLOZAPINE:

Clozapine is Official in Indian pharmacopoeia (IP 2014), United State Pharmacopoeia (USP NF 2004), European Pharmacopoeia (EP 2014).

Table 2.3: Official method estimation of clozapine

Sr. No.	Drug	Method	Description	Ref. No.
1	Clozapine (IP 2014)	**Titrimetric Method**	0.115 gm, dissolve in 70 ml of glacial acetic acid and titrate with 0.1 M Perchloric acid, determining the end-point potentiometrically. Carry Out a blank titration. 1 ml of 0.1 M Perchloric acid is equivalent to 0.01634 g of $C_{18}H_{19}ClN_4$.	7
2	Clozapine Tablet (IP 2014)	**Liquid Chromatography**	**Detection Wavelength:** 257 nm **Mobile Phase:** Methanol: Water: Triethylamine (800:200:0.75 v/v/v) **Stationary Phase:** Stainless steel column 25 cm × 4.0 mm, packed with Octylsilane bonded to porous silica (5 µm) **Flow Rate:** 1 ml/min	7
3	Clozapine (USP NF 2004)	**Titrimetric Method**	115 mg, dissolve in 70 ml of glacial acetic acid and titrate with 0.1 M Perchloric acid, determining the end-point potentiometrically. Carry Out a blank titration.	31

			1 ml of 0.1 M Perchloric acid is equivalent to 16.34 mg of $C_{18}H_{19}ClN_4$.	
4	Clozapine (EP 2014)	**Titrimetric Method**	0.100 g in 50 ml of anhydrous acetic acid. Titrate with 0.1 M Perchloric acid, determining end-point potentiometrically. 1 ml of 0.1 M Perchloric acid is equivalent to 16.34 mg of $C_{18}H_{19}ClN_4$.	32

TABLE 8: REPORTED METHOD OF CLOZAPINE

Sr. No.	Drug	Method	Description	Ref. No.
1	Clozapine in Bulk & tablet dosage forms	**RP-HPLC Method**	**Detection Wavelength:**290 nm **Mobile Phase:** Acetonitrile: Phosphate buffer (70:30% v/v) **Stationary Phase:**C_{18} column (250×4 internal diameter in isocratic mode) **Linearity Range:**1-5 µg/ml **Retention Time:**3.06 min **Flow Rate:**1 ml/min **% Recovery:**97.85 to 101.45% **LOD:**0.1 µg/ml **LOQ:**0.5 µg/ml	33
2	Clozapine in Human plasma	**HPLC-UV Method**	**Detection Wavelength:**250 nm **Mobile Phase:**acetonirile: Methanol: 0.5% triethylamine (40:10:50) **Stationary Phase:**ODS hyoersil (5µm) cartridge column (125×4mm I.D.) **Linearity Range:**Drug-free human plasma concentration- 25-2000 ng/ml Drug- human plasma concentration- 75-1500 ng/ml **Flow Rate:**1 ml/min **LOQ:**25 mg/ml	34
3	Clozapine in Human plasma	**HPLC-UV Method**	**Detection Wavelength:** 250 nm **Internal Standard:** amino-acetophenone **Mobile Phase:** Acetonitrile (30%)- 29 mM Phosphate buffer **Stationary Phase:**CTO-10ASC18 column (25×4.6×5 µ) **Linearity Range:** 20-2000 ng/ml **Flow Rate:** 1 ml/min **Liquid-Liquid extraction:** Diethyl ether	35
4	Clozapine in Tablet and in biological fluids	**UV-VIS Spectrophometer Method using Ion-Pair Complex**	**Detection Wavelength:** 514 nm **Linearity Range:** 2-18 µg/ml **Coloring Agent:** Erichrome black T (EBT) **Solvent:** For Tablet:Sulphuric Acid For Human Serum and Urine: Acetonitrile	36
5	Clozapine in tablets and in Urine	**Spectrophotometric and Fluorimetric Method**	**A) Spectrophptometric Method:** **σ-acceptor:** Iodine **π-acceptor:** 7,7,8,8-	37

			tetracyanoquinondimethane (TCNQ), 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (DDQ), tetracyanoethane (TCNE), p-chloranilic acid (pCA) **Detection Wavelength:** Iodine: 365 nm TCNQ: 843 nm DDQ: 460 nm TCNE: 414 nm pCA: 520 nm **Linearity Range:** 4-200 µg/ml **LOD:** Iodine: 1.12 µg/ml TCNQ: 176 µg/ml DDQ: 2.22 µg/ml TCNE: 0.95 µg/ml pCA: 13.26 µg/ml **B) Fluorimetric Method:** **Detection Wavelength:** $\lambda_{excitation}$-260 nm $\lambda_{emission}$– 355 nm **Solvent:** 1 M Suphuric Acid **Linearity Range:** 24-250 ng/ml **LOD:**6.69 ng/ml	
6	Clozapine, Norclozapine in various biological fluids	**HPLC-UV Method**	**Detection Wavelength:** 254 nm **Internal Standard:** Loxapine **Mobile Phase:** 10 mM Ammonium acetate: Acetonitrile: Methanol (5:3:2 v/v/v) **Stationary Phase:** C6 Phenyl column (3 µm, 2×150 mm)	38
7	Clozapine, Desmethylclozapine and Clozapine N-oxide in Human Plasma	**HPLC-UV Method**	**Detection Wavelength:** 254 nm **Internal Standard:** Triprolidine **Mobile Phase:** Acetonitrile: 0.06 M Phosphate buffer (48:52 v/v) **Stationary Phase:** 250×4.60 mm I.D. analytical column packed with 5 µ C6 silica particles **Flow rate:** 1 ml/min **Liquid-Liquid Extraction:** n-hexane: isoamyl alcohol (75:25 v/v) Organic phase back extracted with 150 microl of 0.1 M dibasic phosphate	39
8	Lamotrigine and Clozapine	**UV Spectroscopic method** **Q Absorbance Ratio Method**	**Detection Wavelength:** Lamotrigine: 307 nm Clozapine: 360 nm **Solvent:** Methanol **Linearity Range:** Lamotrigine: 1-5 µg/ml Clozapine: 6-30 µg/ml **Correlation coefficient:**	40

			Lamotrigine: 0.9992 Clozapine: 0.993 **LOD:** Lamotrigine: 0.259 µg/ml Clozapine: 0.205 µg/ml **LOQ:** Lamotrigine: 0.786 µg/ml Clozapine: 0.679 µg/ml	
9	Clozapine(CLZ), Olanzapine(OLZ), Risperidone(RIP), Quetiapine(QTP) in plasma	**HPLC-MS/ESI Method**	**Detection Wavelength:** **Mobile Phase:** Formic Acid(2.70 mmol/l), Ammonium Acetate(10 mmol/l) in water – Acetonitrile (53:47) **Stationary Phase:**C_{18} (2 mm×125 mm, 3 µm) **Linearity Range:** CLZ: 20-1000 ng/ml OLZ: 1-50 ng/ml RIP: 1-50 ng/ml QTP: 20-1000 ng/ml **Retention Time:** CLZ: 0.9903 OLZ: 09993 RIP: 0.9979 QTP: 0.9985 **Flow Rate:**0.16 ml/min	41

Conclusion:

This review depicts the reported Spectrophotometric and Chromatographic methods; developed and validated for estimation of Atypical Antipsychotics. According to the literature review it was concluded that for Clozapine and Aripiprazole different Spectroscopic & Chromatographic methods are available for Single component as well as for combination. This all methods found to be simple, accurate, economic, precise, and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

There is no reported method for Aripiprazole and Clozapine in synthetic mixture. So there will be a great scope for development of highly Precise, Accurate, Simple as well as rapid analytical methods for latest drugs such as Aripiprazole and Clozapine.

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