

ONLINE SUPPLEMENTARY DOCUMENT

Title: Drug supply and assurance: a cross-sectional study of drug shortage monitoring varieties in China

Authors: Yipeng Lan¹, Xiaofeng Lin¹, Qiannan Chen¹, Li Wang¹, Lihua Sun^{1,2*}, Zhe Huang^{1,2*}

1 School of Business Administration, Shenyang Pharmaceutical University, Shenyang, China

2 Institute of Drug Regulatory Science, Shenyang Pharmaceutical University, Shenyang, China

* Correspondence: Zhe Huang (huangzhe2000@sina.com); Lihua Sun (slh-3632@163.com)

Table S1 Reform of China's Shortage Drug Supply Security Policies

No.	Release time	Policy title	Publishing department	Key content on security of supply of shortage drugs
1	April 8, 2008	Study on the Price of Inexpensive Drugs in Shortage	NDRC	The situation of the shortage of inexpensive drugs and the reasons for the shortage of drugs in China from 2002 to 2007 are explained.
2	November 11, 2015	Announcement on Certain Policies for the Review and Approval of Drug Registration	CFDA	Encourage the research development and production of shortage drugs in the market, establish a regular communication mechanism for shortage drugs, and put forward proposals to speed up the approval of shortage drugs.
3	December 21, 2016	Notice on Matters Relating to the Pilot Program of Designated Production of Clinically Necessary, Low-volume, Market-supplied Shortage Drugs	NHFPC	Proposing to carry out pilot projects for the designated production of clinically necessary medicines, in small quantities and short supply in the market, and completing the bidding process for the designated production of three varieties of Digoxin Oral Solution, Compound Sulphamethoxazole Injection, and Sodium Para-Aminosalicylate for Injection.
4	June 28, 2017	Implementation Opinions on Reforming and Improving the Mechanism for	NHFPC	Measures such as improving the system of monitoring and early warning of drug shortages and list management, establishing a

		Guaranteeing the Supply of Shortage Drugs		hierarchical linkage response mechanism for the supply and security of drugs in shortage, and implementing a categorized and precise policy for the supply and security of shortage drugs have been stipulated.
5	November 16, 2017	Guidelines on Price Behavior for Operators of Shortage Drugs and APIs	NDRC	It proposed measures to regulate the market price behavior of shortage drugs and APIs, maintain the market price order, and establish a fair and competitive market environment for the production, purchase, and sale of drugs and APIs.
6	January 19, 2018	Notice on Organizing and Carrying Out the Construction of Centralized Production Bases for Small Variety Drugs (Shortage Drugs)	MIIT	Combined with the demand for drug supply security and the national layout of centralized production bases, about five enterprises will be selected and recognized for the construction of centralized production bases for small-variety drugs (shortage drugs).
7	July 25, 2019	Circular on the Issuance of Technical Guidelines on Classification and Substitution of Drugs in Shortage in Medical Institutions	NHC	Guiding medical institutions to carry out categorized and graded assessments of clinically necessary drugs in shortage, and carrying out the scientific selection of alternative medicines, to safeguard clinical therapeutic needs and standardize their use. It has standardized the assessment of information on the shortage of medicines and the selection of alternative medicines.
8	August 27, 2019	Drug Administration Law of the People's Republic of China	NPC	A special chapter was devoted to the stockpiling and management of medicines, requiring the State to implement a list management system for shortage drugs.
9	October 15, 2019	Opinions on Further Improving the Work of Guaranteeing the Supply and Stabilizing the Price of Shortage Drugs	GOSC	It is required to improve the sensitivity and timeliness of monitoring and response, to strengthen the provision and use of basic medicines and the standardized management of medication in medical institutions, and to improve the procurement of shortage medicines.
10	April 24, 2020	Circular on the Issuance of Measures for the Management of the National Shortage	NHC	Proposed a management method for the national list of shortage drugs, issued a provincial (municipal, district, and county) information report

		Drug List (for Trial Implementation)		on shortage drugs, and for the first time provided an official definition of shortage drugs.
11	July 8, 2020	Working Procedures for Priority Review and Approval of Drug Marketing Authorization (for Trial Implementation)	NMPA	It has clarified that when applying for marketing authorization for medicines, shortage drugs that are urgently needed clinically will be included in the priority review and approval procedure.
12	December 30, 2020	Circular on the Issuance of a National Shortage Drug List	NHC	Released China's first national list of shortage drugs (including 6 drugs) and the first national key monitoring list of clinically necessary drugs susceptible to shortage (including 57 drugs).
13	November 17, 2021	Measures for the Management of National Medical Stockpile (Revised in 2021)	MIIT	Require a drug stockpiling model that combines various forms of stockpiling, such as physical stockpiling and production capacity stockpiling, for shortage drugs.
14	August 9, 2022	Circular on Strengthening the Monitoring of Production Reserves of Drugs in Shortage and Selected Drugs in the Centralized Volume-based Procurement of Drugs by State Organizations	MIIT	Released China's second list of key monitoring varieties of shortage drugs, covering 980 drug preparations and 256 APIs, the most comprehensive list of key monitoring varieties of shortage drugs to date.

Note: The publishing department here mainly refers to the department at the top of the list. NDRC, National Development and Reform Commission; CFDA, China Food and Drug Administration (changed to the National Medical Products Administration in 2018); NHFPC, National Health and Family Planning Commission (changed to the National Health Commission in 2018); MIIT, Ministry of Industry and Information Technology; NHC, National Health Commission; NPC, National People's Congress; GOSC, General Office of the State Council; NMPA, National Medical Products Administration

Table S2 Detailed information on monitored drugs with multiple ATC codes

No.	Drug name	Number of enterprises included in monitoring	Indications	ATC classification
1	Compound Mannitol Injection	14	Cerebral edema, high intraocular pressure, hypoproteinemia	B (Blood and blood forming organs)
			Nephrotic syndrome, cirrhotic ascites	A (Alimentary tract and metabolism)
2	Magnesium Sulfate Injection	21	Hypertension in pregnancy, convulsions	C (Cardiovascular system)
			Pre-eclampsia, Eclampsia	G (Genito urinary system and sex hormones)
3	Tretinoin Tablets	3	Keratosis pilaris, lichen planus, multiple common warts, erythematous furuncle, acne	D (Dermatological)
			Oral mucosal leukoplakia, acute promyelocytic leukemia, ichthyosis, psoriasis	L (Antineoplastic and immunomodulating agents)
4	Magnesium Sulfate for Injection	1	Hypertension in pregnancy, convulsions	C (Cardiovascular system)
			Pre-eclampsia, eclampsia	G (Genito urinary system and sex hormones)

Table S3 Comparison of the 2020 version of the monitoring list and the 2022 version of the monitoring list, and the number of existing drug manufacturers

No.	2020 version of the National Key Monitoring List of Clinically Essential Drugs Vulnerable to Shortage		2022 version of the List of Drugs in Shortage Monitoring Varieties			Number of drug manufacturers in 2024 (as of March 2024)	Increase or decrease in the number of manufacturers
	Name of drug species	Dosage form	Generic name	Number of corresponding manufacturers/market authorization holders	Whether within the 2020 version of the list		
1	Benzathine Benzylpenicillin	Injection	Benzathine Benzylpenicillin for Injection	6	Yes	6	0
2	Clofazimine	Capsule	Clofazimine Soft Capsules	1	Yes	1	0
3	Allopurinol	Tablet	Allopurinol Tablets	14	Yes	14	0
			Compound Allopurinol Tablets	1	Yes	1	0
			Allopurinol Sustained-release Tablets	1	Yes	1	0
4	Neostigmine	Injection	Neostigmine Methylsulfate Injection	5	Yes	7	+2
			Neostigmine Methylsulfate for Injection	1	Yes	1	0
5	Pyridostigmine Bromide	Tablet	Pyridostigmine Bromide Tablets	3	Yes	3	0
6	Phenobarbital	Injection	Sodium Phenobarbital	4	Yes	5	+1

			Injection				
			Phenobarbital Sodium for Injection	2	Yes	2	0
7	Mannitol	Injection	Mannitol Injection	144	Yes	149	+5
			Compound Mannitol Injection	14	Yes	15	+1
			Oxaliplatin and Mannitol Injection	3	Yes	3	0
			Paracetamol and Mannitol Injection	2	Yes	3	+1
			Fleroxacin and Mannitol Injection	1	Yes	1	0
			Ofloxacin and Mannitol Injection	1	Yes	1	0
8	Nikethamide	Injection	Nikethamide Injection	18	Yes	29	+11
9	Lobeline	Injection	Lobeline Hydrochloride Injection	10	Yes	12	+2
10	Diazepam	Injection	Diazepam Injection	20	Yes	23	+3
11	Nitroglycerine	Tablet, Injection	-	-	No	33	-
12	Propafenone	Injection	Propafenone Hydrochloride Injection	6	Yes	6	0
13	Amiodarone	Injection	Amiodarone Hydrochloride Injection	7	Yes	9	+2
			Amiodarone Hydrochloride For Injection	1	Yes	2	+1

14	Verapamil	Injection	Verapamil Hydrochloride Injection	6	Yes	9	+3
			Verapamil Hydrochloride for Injection	1	Yes	1	0
15	Digoxin	Oral Solution	Digoxin Oral Solution	3	Yes	2	-1
16	Deslanoside	Injection	Deslanoside Injection	3	Yes	3	0
17	Sodium Nitroprusside	Injection	Sodium Nitroprusside for Injection	11	Yes	11	0
			Sodium Nitroprusside Injection	1	Yes	1	0
18	Magnesium Sulfate	Injection	Magnesium Sulfate Injection	21	Yes	30	+9
			Magnesium Sulfate for Injection	1	Yes	1	0
			Magnesium Sulfate Glucose Injection	1	Yes	1	0
19	Phentolamine	Injection	Phentolamine Mesylate Injection	7	Yes	8	+1
			Phentolamine Mesylate for Injection	3	Yes	3	0
20	Epinephrine	Injection	Epinephrine Hydrochloride Injection	22	Yes	23	+1
			Procaine and Adrenaline Injection	11	Yes	13	+2
			Phenylephrine Hydrochloride Injection	2	Yes	4	+2
			Articaine Hydrochloride and	2	Yes	2	0

			Epinephrine Tartrate Injection				
			Mepivacaine Hydrochloride and Adrenaline Injection	1	Yes	1	0
21	Norepinephrine	Injection	Noradrenaline Bitartrate Injection	7	Yes	11	+4
22	Isoproterenol	Injection	Isoproterenol Hydrochloride Injection	2	Yes	2	0
			Isoprenaline Sulfate Injection	1	Yes	1	0
23	Dopamine	Injection	Dopamine Hydrochloride Injection	8	Yes	25	+17
			Dopamine hydrochloride for Injection	2	Yes	2	0
24	Dobutamine	Injection	Dobutamine Hydrochloride Injection	23	Yes	26	+3
			Dobutamine Hydrochloride and Glucose Injection	3	Yes	3	0
			Dobutamine Hydrochloride for Injection	2	Yes	2	0
25	Atropine	Injection	Atropine Sulfate Injection	88	Yes	98	+10
			Atropine Sulfate and Promethazine Hydrochloride Injection	2	Yes	2	0
			Morphine and Atropine Sulfate Injection	1	Yes	1	0
26	Arginine	Injection	Arginine Hydrochloride	8	Yes	9	+1

			Injection				
			Arginine Acetylsalicylate for Injection	5	Yes	5	0
			Arginine Hydrochloride for Injection	4	Yes	4	0
			Arginine Glutamate Injection	1	Yes	1	0
			Arginine Hydrochloride and Glucose Injection	1	Yes	2	+1
27	Furosemide	Injection	Furosemide Injection	58	Yes	66	+8
			Furosemide for Injection	4	Yes	3	-1
28	Thrombin	Lyophilizing Powder	Lyophilizing Thrombin Powder	19	Yes	19	0
			Human Prothrombin Complex	2	Yes	2	0
			Thrombin	2	Yes	2	0
			Human Thrombin for External use, Freeze-dried	1	Yes	1	0
29	Vitamin K1	Injection	Vitamin K1 Injection	13	Yes	13	0
30	Protamine	Injection	Protamine Sulfate Injection	3	Yes	3	0
31	Urokinase	Injection	Urokinase for Injection	3	Yes	29	+26
			Recombinant Human Urokinase for Injection	1	Yes	1	0
32	Hydrocortisone	Injection	Hydrocortisone Injection	48	Yes	57	+9
			Hydrocortisone Sodium Succinate for Injection	4	Yes	4	0
			Hydrocortisone Acetate	1	Yes	1	0

			Injection				
33	Corticotropin	Injection	Corticotropin for Injection	2	Yes	2	0
34	Thiamazole	Tablet	Thiamazole Tablets	15	Yes	15	0
			Thiamazole Enteric-coated Tablets	1	Yes	1	0
35	Cyclophosphamide	Injection	Ifosfamide for Injection	18	Yes	16	-2
			Cyclophosphamide for Injection	5	Yes	4	-1
36	Methotrexate	Injection	Methotrexate for Injection	11	Yes	11	0
			Methotrexate Injection	2	Yes	3	+1
37	Mercaptopurine	Tablet	Mercaptopurine Tablets	6	Yes	7	+1
38	Cytarabine	Injection	Cytarabine Hydrochloride for Injection	5	Yes	5	0
			Cytarabine for Injection	2	Yes	3	+1
39	Mitoxantrone	Injection	Mitoxantrone Hydrochloride for Injection	6	Yes	6	0
			Mitoxantrone Hydrochloride Liposome Injection	1	Yes	1	0
			Mitoxantrone Hydrochloride Injection for Tracing	1	Yes	1	0
			Mitoxantrone Hydrochloride Injection	1	Yes	2	+1
			Mitoxantrone Hydrochloride Sodium Chloride Injection	1	Yes	1	0
40	Etoposide	Injection	Etoposide Injection	13	Yes	15	+2
			Etoposide Phosphate for	2	Yes	2	0

			Injection				
			Etoposide for Injection	1	Yes	1	0
41	Bleomycin A5 (Pingyangmycin)	Injection	Bleomycin A5 Hydrochloride for Injection	3	Yes	3	0
42	Mitomycin	Injection	Mitomycin for Injection	4	Yes	3	-1
43	Bleomycin	Injection	Bleomycin Hydrochloride for Injection	2	Yes	2	0
44	Vincristine	Injection	Vincristine Sulfate for Injection	9	Yes	9	0
45	Tretinoin	Tablet	Tretinoin Tablets	3	Yes	2	-1
46	Calcium Gluconate	Injection	Calcium Gluconate Injection	51	Yes	62	+11
			Calcium Gluconate and Sodium Chloride Injection	1	Yes	6	+5
47	Sodium Thiosulfate	Injection	Sodium Thiosulfate Injection	3	Yes	5	+2
			Sodium Thiosulfate for Injection	1	Yes	1	0
48	Pralidoxime Chloride	Injection	Pralidoxime Chloride Injection	7	Yes	7	0
			Compound Pralidoxime Chloride Injection	1	Yes	1	0
49	Methylthioninium Chloride	Injection	Methylthioninium Chloride Injection	4	Yes	3	-1
50	Naloxone	Injection	Naloxone Hydrochloride Injection	25	Yes	25	0
			Naloxone Hydrochloride for Injection	13	Yes	13	0

51	Acetamide	Injection	Acetamide Injection	1	Yes	1	0
52	Penicillamine	Tablet	Penicillamine Tablets	3	Yes	3	0
53	Sodium Dimercaptopropane Sulfonate	Injection	Sodium Dimercaptopropane Sulfonate Injection	3	Yes	3	0
54	Snake Antivenins	Injection	-	-	No	0	-
55	Oxytocin	Injection	Oxytocin Injection	19	Yes	38	+19
			Carbetocin Injection	7	Yes	9	+2
			Oxytocin for Injection	2	Yes	3	+1
56	Posterior Pituitary	Injection	Posterior Pituitary Injection	7	Yes	9	+2
57	Ethacridine	Injection	Ethacridine Lactate Injection	4	Yes	4	0
			Ethacridine Lactate for Injection	1	Yes	1	0

Table S4 Detailed information on shortage medicines for which exclusive production exists

No.	Generic name	Manufacturer	Indications	Drug specifications	Approval number
1	Compound Pralidoxime Chloride Injection	Beijing Huasu Pharmaceutical Co., Ltd.	Organophosphorus pesticide poisoning.	2ml:Chlorophosphamide 0.4g,Atropine Sulfate 3mg,Benactyzine Hydrochloride 3mg.	H11022547
2	Isoprenaline Sulfate Injection	China Resources Double-Crane Pharmaceutical Co.,Ltd.	Cardiac arrest; infectious shock; cardiogenic shock; complete atrioventricular block.	2ml:1mg	H11020788
3	Ethacridine Lactate for Injection	China Resources Double-Crane Pharmaceutical Co.,Ltd.	Induce labor (childbirth).	0.1g(Isacridine lactate anhydrous)	H11022105
4	Mitoxantrone Hydrochloride Liposome Injection	CSPC Zhongnuo Pharmaceutical (Shijiazhuang) Co., Ltd.	Relapsed/refractory peripheral T-cell lymphoma.	10ml:10mg (based on C ₂₂ H ₂₈ N ₄ O ₆)	H20220001
5	Clofazimine Soft Capsules	Shanxi Liye Pharmaceutical Co., Ltd.	Infection with sulfone-resistant strains; verrucous leprosy; drug-induced acute leprosy reactions; AIDS complicating atypical mycobacterial infections; erythema nodosum of leprosy.	50mg	H32021093
6	Morphine and Atropine Sulfate Injection	Northeast Pharmaceutical Group Shenyang No.1 Pharmaceutical Co., Ltd	Anesthesia; reflex cardiac arrest during anesthesia.	Morphine Hydrochloride 10mg,Atropine Sulfate 0.5mg	H21021924
7	Arginine Glutamate	Liaoning Haisco	Elevated blood ammonia due to chronic	200ml:20g	H20150032

	Injection	Pharmaceutical Co., Ltd.	liver disease.		
8	Magnesium Sulfate for Injection	Liaoning Pharm-Link Pharmaceutical Co., Ltd.	Eclampsia; preterm labor; gestational hypertension; preeclampsia.	2.5g	H20051792
9	Hydrocortisone Acetate Injection	Shanghai General Pharmaceutical Co. Ltd.	Allergic diseases; critical toxic infections; hypopituitarism; inflammatory diseases; adrenocortical insufficiency.	5ml:0.125g	H31021400
10	Recombinant Human Urokinase for Injection	Tasly Pharmaceutical Group Co., Ltd.	Acute ST-segment elevation myocardial infarction.	5mg(500,000IU)/strip	S20110003
11	Neostigmine Methylsulfate for Injection	Jiangsu Jiuxu Pharmaceutical Co., Ltd.	Myasthenia gravis; urinary retention; postoperative functional bowel distension.	1mg	H20040691
12	Ofloxacin and Mannitol Injection	Henan Yonghe Pharmaceutical Co., Ltd.	Complicated urinary tract infections; typhoid fever; cervicitis; respiratory tract infections; simple urinary tract infections; gastrointestinal tract infections; infections of the skin and skin structures; lung infections caused by gram - bacteria; bone and joint infections; gonorrheal urethritis; septicemia; acute bronchitis caused by gram - bacteria; bacterial prostatitis; infections of the genitourinary system; infections with sensitive bacteria.	100ml:Ofloxacin 0.2g with mannitol 5.3g	H10950145
13	Human Thrombin for External use, Freeze-dried	Hualan Biological Engineering, Inc.	Postoperative bleeding.	500IU/1ml/vial	S20050092
14	Compound Allopurinol	Guangdong Shixin	Hyperuricemia; gout.	Each tablet contains 100mg of	H20094159

	Tablets	Pharmaceutical Co., Ltd.		Allopurinol and 20mg of Benzbromarone.	
15	Sodium Nitroprusside Injection	Hainan Puli Pharmaceutical Co., Ltd.	Hypertensive crisis; acute congestive heart failure.	2 ml:50 mg [as $\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}]\cdot 2\text{H}_2\text{O}$]	H20223226
16	Allopurinol Sustained-release Tablets	Hainan Puli Pharmaceutical Co., Ltd.	Gout; gout stones; uric acid kidney stones; uric acid nephropathy; hyperuricemia.	0.25g	H20041743
17	Mitoxantrone Hydrochloride Sodium Chloride Injection	Sichuan Meida Kanghuakang Pharmaceutical Co., Ltd.	Prostate Cancer; Colorectal Cancer; Testicular Tumors; Kidney Cancer; Melanoma; Breast Cancer; Ovarian Cancer; Multiple Myeloma; Malignant Lymphoma; Acute Leukemia; Hepatocellular Cancer; Head and Neck Malignancies; Endometrial Cancer; Soft Tissue Sarcoma; Lung Cancer.	100ml:5mg	H10980248
18	Thiamazole Enteric-coated Tablets	Guizhou Shengjitang Pharmaceutical Co., Ltd.	Hyperthyroidism.	10mg	H20080775
19	Etoposide for Injection	Yunnan Botanical Pharmaceutical Co., Ltd.	Neuroblastoma; gastric cancer; rhabdomyosarcoma; small cell lung cancer; malignant lymphoma; malignant germ cell tumor; esophageal cancer; leukemia; non-small cell lung cancer; ovarian cancer.	40mg	H20060014
20	Mepivacaine Hydrochloride and Adrenaline Injection	SEPTODONT	Oral local infiltration anesthesia; dental local infiltration anesthesia.	1.8ml/strip	HJ20171134
21	Verapamil Hydrochloride for Injection	Jilin Jinsheng Pharmaceutical Co. Ltd.	Paroxysmal supraventricular tachycardia; atrial flutter; atrial fibrillation.	5mg	H20031345
				10mg	H20031346
22	Sodium Thiosulfate for	Shanghai ShangPharma	Iodine poisoning; lead poisoning; cyanide	0.32g	H31020533

	Injection	Xinya Pharmaceutical Co. Ltd.	poisoning; arsenic poisoning; mercury poisoning; bismuth poisoning.	0.64g	H31020534
23	Magnesium Sulfate Glucose Injection	Shanghai Changzheng Fumin Jinshan Pharmaceutical Co., Ltd.	Spasms; convulsions; preeclampsia; moderate to severe gestational hypertension; eclampsia.	100ml: magnesium sulfate 1g, glucose 5g	H20020017
				250ml: magnesium sulfate 2.5g, glucose 12.5g	H20020018
24	Fleroxacin and Mannitol Injection	Jiangsu Inbesi Technology Development Co., Ltd.	Gynecologic infections; Allergenic infections; Respiratory infections; Digestive infections; Soft tissue skin infections; Sepsis; Enterobacteriaceae infections (genus); Genitourinary infections.	100ml: Floxacin 0.2g, Mannitol 5g	H20020610
				100ml: Floxacin 0.4g with mannitol 5g	H20000452
25	Mitoxantrone Hydrochloride Injection for Tracing	Shanghai Truno Pharmaceutical Co., Ltd.	Lymph node tracing in thyroid cancer.	0.5ml:2.5mg	H20237085
				1ml : 5mg	H20227061
				2ml:10mg	H20210025
26	Acetamide Injection	Shandong Xinhua Pharmaceutical Co., Ltd.	Sodium fluoroacetate poisoning; fluoroacetamide poisoning; glycofluoride poisoning.	5ml:2.5g	H37023213
				2ml:1g	H37023214
				10ml:5g	H37023215

Table S5 Detailed information on exclusively manufactured varieties of APIs included in monitoring

No.	API Name	Manufacturer	Registration number	Results of the joint review with durg preparations	Approval number
1	Dibrommannitol	Beijing Saier Biological Pharmaceutical Co., Ltd.	Y20190007437	A	H11021217
2	Corticotrophin	Shanghai ShangPharma No.1 Biochemical Pharmaceutical Co., Ltd.	Y20190002770	A	H31022942
3	Sodium Dimercaptopropane Sulfonate	Shanghai Wanxiang Pharmaceutical Co., Ltd.	Y20220001130	I	/
			Y20190001405	A	H20033618
4	Bleomycin Hydrochloride	Zhejiang Hisun Pharmaceutical Co., Ltd.	Y20190001866	A	H20051232
5	Mitoxantrone	Brilliant Pharmaceutical Co. Ltd.	Y20190005755	A	H10960189

Note: Results of the co-review with the durg preparation: A indicates raw materials/excipients/packaging materials that have been approved for use in the listed preparation, and I indicates raw materials/excipients/packaging materials that have not yet passed the co-review and approval with the preparation.