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# Supply chain vulnerabilities of high-use pharmaceuticals: An explorative cohort study

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2 3		
4	2	SUPPLY CHAIN VULNERABILITIES OF HIGH-USE PHARMACEUTICALS: AN EXPLORATIVE
5 6	3	COHORT STUDY
0 7	4	Doerine J Postma, *1.2 Peter AGM De Smet, <sup>3</sup> Aukje K Mantel-Teeuwisse, <sup>1</sup> Hubert GM Leufkens, <sup>1</sup> Kim
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21		
22 23	16	ABSTRACT
24	17	Objectives – To assess the upstream pharmaceutical supply chains of ten high-use pharmaceuticals
25 26	18	to detect vulnerabilities that may increase the risk of medicine shortages
20 27	19	Design – Explorative cohort study
28	20	Setting – Dutch outpatient setting in 2022
29 30	21	Participants – A total of 407 authorised medicinal products for ten pharmaceutical substances with
31	22	the largest number of outpatients
32 33	23	Main outcome measures – The diversity of active pharmaceutical ingredient (API) and finished
34	24	pharmaceutical product (FPP) manufacturers, their geographic locations and the interdependencies
35 36	25	between these manufacturers and marketing authorisation holders (MAHs)
37	26	Results – For the 407 authorised medicinal products, 50 of the 90 API manufacturing sites were in
38 39	27	Asia, and 38 in Europe. For five pharmaceutical substances, most of the API sites were located
40	28	outside Europe. Of the 128 FPP manufacturing sites, 94 were in Europe, and 31 in Asia. For all ten
41 42	29	substances, at least 47% of FPP sites were located in Europe.
42 43	30	API manufacturing for 122 of the 407 products (30%) was entirely performed outside Europe,
44	31	and FPP manufacturing for 66 of the 407 products (16%). For four substances, more than half of the
45 46	32	products depended on API manufacturing outside Europe.
47	33	The number of distinct API and FPP manufacturing sites per substance was at least four. For
48 49	34	amoxicillin, 16 of the 32 products (50%) entirely depended on one and the same API site. For
49 50	35	omeprazole, 39 of the 85 products (46%) entirely depended on one and the same FPP site.
51	36	MAHs applied dual sourcing for API and FPP manufacturing for 61 (15%) of the authorised
52 53	37	medicinal products. For three pharmaceutical substances, none of the authorised medicinal products
54	38	listed at least two API and FPP manufacturing sites.
55 56	39	Conclusion – Our study of the supply chains of high-use pharmaceutical substances indicates the
57	40	need for a granular assessment of the interdependencies between MAHs, API and FPP
58 59 60	41	manufacturers to identify upstream supply chain vulnerabilities.

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1 2		
2 3 4	42	STRENGTHS AND LIMITATIONS
5	43	- This study offers insights into the pharmaceutical supply chains, focussing on the diversity
6 7	44	of API and FPP manufacturers and their geographic locations.
8	45	- The use of Dutch Medicines Evaluation Board database to analyse the research question
9	46	is ideal since this is the official source to register this information.
10 11	47	- We visualised the ten upstream pharmaceutical supply chains using Sankey
12	48	diagrams, illustrating the complex interdependencies among stakeholders.
13 14	49	- Our cohort of ten pharmaceutical substances is unlikely to be representative of all
15	50	medicines.
16 17		
18 19	51	
20	52	SUMMARY BOX
21 22	53	What is already known on this topic
23	54	- The pharmaceutical supply chain is highly complex, involves multiple interdependent
24 25	55	stakeholders, relies on a global network, and lacks transparency.
26	56	- Upstream supply-related issues (i.e. manufacturing and quality) are among the main causes of
27 28	57	medicine shortages.
29	58	What this study adds
30 31	59	- A minority of the high-use authorized medicinal products studied were entirely depended on API
32	60	and FPP manufacturing sites outside of Europe. However, for some pharmaceutical substances,
33	61	most of the authorized medicinal products entirely relied on non-European API manufacturers.
34 35	62	- A viable market with different API and FPP manufacturers was established for all studied
36	63	substances, but there was an overdependency on one API or FPP manufacturer for some
37 38	64	substances.
39	65	- Dual sourcing for API and FPP manufacturing was adopted for only a limited share of authorised
40 41	66	medicinal products, and for some substances, none of the authorised products listed dual sourcing
42	67	for both the API and FPP.
43 44		for both the API and FPP.
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3 4	68	INTRODUCTION
5	69	A continuous supply of quality-assured, safe, effective, and affordable medicines is essential
6	70	for a well-functioning health system. [1] Until the beginning of the 21 <sup>st</sup> century the availability of
7 8	71	medicines did not significantly concern high-income countries. Then, discrepancies between supply
9	72	and demand began to frequently emerge. [2-4] Currently, medicine shortages are 'the new normal'. [5,
10 11	73	6]. The main causes of medicine shortages are related to manufacturing and quality issues [7, 8],
12	74	which are part of the upstream supply chain, from active pharmaceutical ingredient (API) to FPP
13	75	manufacturing and packaging, rather than the downstream distribution. [9] Despite the increased focus
14 15	76	on the availability of medicines during the COVID-19 pandemic, shortages further increased post-
16	77	COVID-19, [10-12] underscoring the necessity of addressing the ongoing challenges in the
17 18	78	pharmaceutical supply chain.
19	79	The pharmaceutical supply chain is complex, involving multiple interdependent stakeholders
20 21	80	and relying on a global distribution network. MAHs are responsible for their authorised medicinal
21	81	products and for the qualification and selection of the involved (number of) manufacturers. MAHs often
23	82	rely on manufacturers located worldwide to produce APIs and finished pharmaceutical products
24 25	83	(FPPs). [13] MAHs may decide to manufacture APIs and FPPs in-house, which offers control over
26	84	quality, quantity, and timelines, thus providing the flexibility to rapidly respond to manufacturing
27 28	85	problems requiring expertise and resources. However, manufacturing generic products is increasingly
29	86	outsourced, enlarging external dependency and introducing complexity into the upstream supply
30 31	87	chain. [14] A much-raised additional concern is the geographical location and concentration of
32	88	manufacturing sites, particularly in Asia. [15-17] Studies on manufacturing sites and their geographic
33	89	locations are limited. For the API market in general, we found data regarding the geographic
34 35	90	distribution of manufacturers in relation to turnover. According to the researchers, API manufacturing
36	91	for the European market is predominantly situated in Asia (56%), followed by Western Europe (24%)
37 38	92	and North America (12%), with limited contributions from the rest of the world (8%). [18]
39	93	The supply chain may be disturbed by manufacturing issues, natural disasters, or geopolitical
40 41	94	disputes. Problems with API availability may disrupt FPP manufacturing, impact the marketing of
42	95	authorised medicinal products by MAHs, prohibit dispensing by the pharmacist, and ultimately restrict
43	96	patient access. A robust supply chain would prevent a problem occurring at one point in the supply
44 45	97	from causing disruptions elsewhere. To enhance supply chain resilience, ensuring supplier diversity is
46	98	considered crucial. [19, 20] For a viable market, a supplier base of at least three different API and FPP
47 48	99	manufacturers per pharmaceutical substance is considered desirable according to participants at a
49	100	WHO-convened technical consultation. [21] Dual sourcing strategies per authorised medicinal product
50 51	101	- establishing two suppliers for a given ingredient or component in a regulatory product dossier - is
52	102	also a well-known measure. [20, 22]
53	103	Supply chain resilience is in the spotlight of global pharmaceutical policies. [17, 23] The
54 55	104	European Commission is analysing supply chains of medicines on the EU list of critical medicines to
56	105	identify vulnerabilities. Foreseen EU policy measures to strengthen these supply chains include
57 58	106	regulatory flexibilities and recommendations to diversify manufacturers and increase Europe's
59	107	manufacturing capacity. [24, 25] Insight into interdependencies among stakeholders – such as the
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number of API manufacturers supplying FPP manufacturers and the subsequent number of FPP manufacturers supplying different MAHs, along with their geographic locations - can help to identify supply chain vulnerabilities. Although geographic concentration is often reported as an issue, and medicine shortages and pharmaceutical supply chain vulnerabilities have been linked by some researchers [26-29], no studies have specifically analysed the interdependencies among stakeholders in the upstream pharmaceutical supply chain.

This research aimed to assess pharmaceutical supply chains by evaluating the diversity of API and FPP manufacturers, their geographic locations and the interdependencies between MAHs and these manufacturers. We selected ten pharmaceutical substances with the largest number of outpatients in the Netherlands since supply disruptions of these medicines may affect a significant share of the population.

1		
2 3	119	METHODS
4 5	120	Study population and data collection
6	121	For this explorative cohort study, ten pharmaceutical substances with the largest number of
7 8	122	patients in the Dutch outpatient setting were chosen because the number of patients is a key element
o 9	123	determining a shortage's impact. [30] All treatments were counted equally, regardless of therapeutic
10	124	use and treatment duration; thus, we did not take the total annual volume into account. The ten high-
11 12	125	use pharmaceutical substances in 2021 originated from the database of the Dutch Foundation for
13	126	Pharmaceutical Statistics [31, 32], which contains complete information on the Dutch outpatient setting
14 15	127	including the outpatient pharmacies in hospitals. The pharmaceutical substances were classified
16	128	according to the WHO's Anatomical Therapeutic Chemical (ATC) classification fifth level (i.e. APIs).
17 18	129	[33] We included pharmaceutical substances containing one or a fixed combination of two active
19	130	components.
20 21	131	The medicinal products containing these ten pharmaceutical substances authorised in the
22	132	Netherlands, along with their responsible MAHs and the involved API and FPP manufacturers and
23 24	133	their geographic locations, were identified using the Dutch Medicines Evaluation Board (MEB) [34]
25	134	database in July 2022. We excluded products for parenteral use such as solution for injection or
26 27	135	infusion since these are mainly prescribed in hospital settings.
27	136	Study outcomes and data analysis
29 30	137	For the authorised medicinal products, a researcher (DJP) obtained distinct MAHs, API and
31	138	FPP manufacturers, and geographic locations of the manufacturers at the country and continent
32	139	levels. The geographic locations were limited to API and FPP manufacturing sites because they are
33 34	140	more geographically bound than MAHs, and regulatory requirements are involved when changing
35	141	them. [35]
36 37	142	We calculated the median number of authorised medicinal products per MAH and the
38	143	interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API
39 40	144	versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical
41	145	substances, we only plotted the manufacturers of the substances with the fewest API manufacturers
42 43	146	because it represented the worst case and, thus, greatest overall vulnerability.
44	147	We mapped the pharmaceutical supply chains using Sankey diagrams containing nodes and
45 46	148	links to visualise stakeholder interdependencies. The nodes represent the API manufacturer, the FPP
47	149	manufacturer, authorised medicinal products, and the MAH, respectively. The links show their
48 49	150	interactions. The width of the nodes is proportional to the number of links; a wider node means more
50	151	interaction with next-stage stakeholders.
51 52	152	Descriptive statistics present the characteristics of authorised medicinal products and
53	153	manufacturing sites. Graphics were created using Microsoft Office 365 Excel and Adobe Illustrator
54	154	(Sankey diagrams).
55 56	155	Patient and Public Involvement
57 58	156 157	Neither patients nor the public were involved in the conception, design, or execution of this study.
59 60		
50		

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#### RESULTS

The ten pharmaceutical substances with the largest number of patients in the outpatient setting in the Netherlands included two ATC fifth-level substances containing more than two active components. These two substances were replaced by the next two ATC fifth-level substances that met the inclusion criteria. For the selected substances, 407 medicinal products for outpatient use were authorised in the Netherlands in July 2022 (Figure 1). In total, 37% of the Dutch population (6.5 million people) received a prescription for one or more of the selected medicinal products (see supplementary table S1).

#### Figure 1: Selection of pharmaceutical substances with the largest number of patients in the Dutch outpatient setting and the related authorised medicinal products for analysis

The 407 products included authorised off-patent medicinal products predominantly intended for oral use (378; 93%), with a few for inhalation (21; 5%) or rectal use (8; 2%). The number of authorised medicinal products per pharmaceutical substance ranged from 21 for levonorgestrel/ethinylestradiol and salbutamol to 85 products for omeprazole. The 407 authorised medicinal products were the responsibility of 70 distinct MAHs (see supplementary table S1), and their manufacturing involved 90 distinct API sites and 128 distinct FPP sites. Three manufacturing sites produced APIs as well as FPPs. In our cohort of 407 products, the 70 MAHs were responsible for a median of three (IQR: 2-6) authorised medicinal products (range: 1-42). Of the 70 MAHs, 49 had marketing authorisations for products for one of the ten pharmaceutical substances. Three MAHs had marketing authorisations for products for nine of the ten pharmaceutical substances.

#### **API** manufacturing

The 90 API manufacturers for the 407 authorised medicinal products were mostly located in Asia (50; 55%), a large minority in Europe (38; 42%), and rarely in the Americas (2; 3%) (see Table 1 and supplementary figure S1). The number of distinct API manufacturing sites per pharmaceutical substance ranged from four for levonorgestrel/ethinylestradiol to 17 for pantoprazole. For desloratadine, diclofenac, metoprolol, pantoprazole, and simvastatin, more than half of the API manufacturing sites were located outside Europe (54%-82%). For amoxicillin and omeprazole, the API sites were equally divided outside and within Europe. For the remaining three substances, a minority of the sites were located outside Europe (range: 0%-40%) thus for the majority within Europe (60–100%). For all pharmaceutical substances at least two API manufacturing sites were located in Europe.

Among the 407 authorised medicinal products, 122 entirely relied on APIs manufactured outside of Europe (Table 1). For four substances (desloratadine, diclofenac, pantoprazole, and simvastatin), the authorised medicinal products predominantly relied on only API manufacturing sites outside of Europe (range: 52-66%). For colecalciferol, metoprolol and omeprazole, the API manufacturing sites were outside and within Europe. For the remaining three substances, the minority of the products relied on API sites outside Europe (range: 0-25%). The number of authorised 

medicinal products per substance specified per country of the manufacturing site is displayed in supplementary figure S1.

Table 1: Number and geographic location (continent) of active pharmaceutical ingredient (API) manufacturing sites and related medicinal products

nharmacoutical	num	ber of API mar sites per cont	•	number of related authorised medicinal products per continent				
pharmaceutical substance	total	Europe	other continents	total	Europe	Europe and other continents*	other continents	
overall	90	38 (42%)	52 (58%)	407	146 (36%)	139 (34%)	122 (30%)	
amoxicillin	6	3 (50%)	3 (50%)	32	24 (75%)		8 (25%)	
colecalciferol	5	3 (60%)	2 (40%)	82	47 (57%)	18 (22%)	17 (21%)	
desloratadine	15	3 (20%)	12 (80%)	34		15 (44%)	19 (56%)	
diclofenac	8	3 (38%)	5 (62%)	29	7 (24%)	3 (10%)	19 (66%)	
levonorgestrel / ethinylestradiol	4 4	4 (100%) 4 (100%)		21	21 (100%)			
metoprolol	13	6 (46%)	7 (54%)	34	13 (38%)	16 (47%)	5 (15%)	
omeprazole	12	6 (50%)	6 (50%)	85	14 (16%)	56 (66%)	15 (18%)	
pantoprazole	17	4 (24%)	13 (76%)	33		16 (48%)	17 (52%)	
salbutamol	6	5 (83%)	1 (17%)	21	20 (95%)		1 (5%)	
simvastatin	11	2 (18%)	9 (82%)	36		15 (42%)	21 (58%)	

\* The regulatory dossier for an authorised medicinal product may list several API manufacturers on different continents.

## FPP manufacturing

The 128 FPP manufacturing sites for the 407 authorised medicinal products were mainly situated in Europe (94; 74%), to a lesser extent in Asia (31; 24%), and rarely in the Americas (3; 2%) (see Table 2 and supplementary figure S1). The number of distinct FPP manufacturing sites per pharmaceutical substance ranged from seven for levonorgestrel/ethinylestradiol to 23 for simvastatin. For pantoprazole a small majority (53%) of FPP sites were located outside Europe and for amoxicillin the FPP sites were equally divided outside and within Europe. For the other eigth substances, the minority of FPP sites were located outside Europe (range: 0-48%). For all ten pharmaceutical substances at least five FPP manufacturing sites were present in Europe.

Of the related authorised medicinal products, 66 of the 407 (16%) were entirely manufactured outside Europe (Table 2). For all substances, the minority of the authorised medicinal products relied solely on FPP manufacturing outside Europe (range: 0-38%). The number of authorised medicinal products per substance specified per country of the manufacturing site is displayed in supplementary figure S1.

## Table 2: Number and geographic location (continent) of finished pharmaceutical product (FPP) manufacturing sites and related medicinal products

pharmaceutical		er of FPP mai sites per cont	-	Number of related authorised medicinal products per continent			
substance	Total	Europe	other continents	total	Europe	Europe and other continents*	other continents
overall	128	94 (73%)	34 (17%)	407	286 (70%)	55 (14%)	66 (16%)

	amoxicillin	10	5 (50%)	5 (50%)	32	23 (72%)		9 (28%)
	colecalciferol	21	17 (81%)	4 (19%)	82	56 (68%)	14 (17%)	12 (15%)
	desloratadine	21 19	15 (71%) 16 (84%)	6 (29%) 3 (16%)	34 29	20 (59%) 24 (83%)	1 (3%) 3 (10%)	13 (38%) 2 (7%)
	diclofenac levonorgestrel/	19		3 (16%)	29		3 (10%)	
	ethinylestradiol	7	6 (86%)	1 (14%)	21	18 (86%)		3 (14%)
	metoprolol	18	14 (78%)	4 (22%)	34	25 (74%)	5 (15%)	4 (12%)
	omeprazole	10	7 (70%)	3 (30%)	85	77 (91%)	3 (3%)	5 (6%)
	pantoprazole	17	8 (47%)	9 (53%)	33	14 (42%)	14 (42%)	5 (16%)
	salbutamol simvastatin	11 23	11 (100%) 12 (52%)	11 (48%)	21 36	21 (100%) 8 (22%)	15 (42%)	13 (36%)
222	* The regulatory dossie		. ,	. ,		、 ,		. ,
223								
224	Diversity of man	ufacture	ers					
225	The regulatory dos	ssiers of	346 of the 4	07 products	(85%) lis	sted either on	e API manufa	cturing and
226	multiple FPP sites	(83; 20	%), one FPF	nanufacturi	ng and n	nultiple API s	ites (157; 39%	6), or one AF
227	and one FPP site	(106; 26	%) (Figure 2	2). For 61 aut	horised r	medicinal pro	ducts (15%), a	at least two /
228	and FPP sites wer	e listed.	For four sul	ostances, mo	st authoi	rised medicin	al products (6	9%–78%) re
229	on one API manuf	acturing	site. For eig	ht substance	s, more	than half of t	he authorised	medicinal
230	products (52%–95	%) relie	d on one FP	P manufactu	ring site	(see supplen	nentary table	<mark>S2</mark> ). For
231	amoxicillin, coleca	lciferol,	and levonor	gestrel/ethiny	lestradio	l, none of the	e authorised p	roducts liste
232	two or more manu	facturing	g sites for the	e APIs and F	PPs ( <mark>see</mark>	e supplement	ary figure S2)	. For
233	simvastatin and pa	antopraz	ole, most of	the authorise	ed medic	inal products	(both 61%) li	sted at least
234	manufacturing site	es for the	e APIs and F	PPs.				
235								
236	Figure 2: Number of	of author	ised medicin	al products w	vith the c	orresponding	number of ma	anufacturing
237	sites of active pha	rmaceuti	cal ingredier	nts (APIs) and	finished	pharmaceuti	cal products (F	FPPs) accord
238	to the Dutch Medic	ines Eva	luation Boar	d database (n	i = 407). <			
239	Red = one manufact	turing site	e for APIs <u>and</u>	FPPs; orange	e = one m	anufacturing s	ite for APIs <u>or</u> F	PPs; green =
240	least two manufactu	ring sites	for APIs and	FPPs.				
241								
242	Interdependency							
243	The flow o	of the ter	n upstream p	harmaceutic	al supply	chains is illu	strated in Sar	nkey diagram
244	showing the journe	ey from	API manufac	cturer to FPP	manufa	cturer, ending	g in an authori	sed medicin
245	product under the	respons	ibility of an I	MAH (see su	oplemen	tary figure S3	3). We identifie	ed two main
246	patterns of supply	chains,	the 'isolated	chain' and th	ne 'intertv	wined chain',	for example,	as depicted
247	the diagrams of de	esloratad	dine (Figure	3A) and simv	astatin (	Figure 3B), r	espectively. T	he isolated
248	chain involves (in	extremis	s) one MAH	depending or	n one AP	I and one FF	P manufactur	er. The
249	intertwined chain of	consists	of multiple A	API and FPP	manufac	turers servin	g multiple MA	Hs.
250	Of the 70	distinct I	MAHs, 11 (1	6%) depende	ed on one	e API manufa	acturer and on	e FPP site

Of the 70 distinct MAHs, 11 (16%) depended on one API manufacturer and one FPP site (isolated chain), 14 (20%) on one API manufacturer and multiple FPP sites, 20 (28%) on multiple API sites and one FPP manufacturer, and 25 (36%) on multiple API and FPP sites (intertwined chain). When an MAH relied on several manufacturers, the same combinations of API and FPP manufacturers (intertwined chain, Figure 3A and B) occurred.

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#### DISCUSSION

#### **Principal findings**

This explorative study on supply chain vulnerabilities of ten high-use pharmaceuticals unravelled several overall existing concerns. For these substances, a significant proportion of the API and FPP manufacturing sites were located in Europe, and an even higher proportion of the related authorised medicinal products listed an API or FPP manufacturing site in Europe. All ten substances had a supplier base exceeding at least three different API and FPP manufacturers, which is desirable for a viable market [21]. Dual sourcing for API and FPP manufacturing, however, was present for a minority of the authorised medicinal products. 

The dependency on API and FPP manufacturing sites in Asia [15, 16] was less pronounced than expected. For the ten substances, 43% and 74% of the API and FPP manufacturing sites, respectively, were located in Europe and were involved in the manufacturing of 68% and 84% of the related authorised medicinal products, respectively. However, for four pharmaceutical substances, more than half of the products (54-67%) did rely on non-European API manufacturers. For each pharmaceutical substance, at least four different API and seven different FPP manufacturers were listed, thus exceeding an supplier base of at least three manufacturers for APIs and FPPs. [21] Nevertheless, some substances were overdependent on one and the same manufacturer, such as amoxicillin (strongly depending on one and the same API manufacturer) and omeprazole (strongly depending on one and the same FPP manufacturer). MAHs had adopted a dual sourcing strategy for API and FPP manufacturing for only 15% of the authorised medicinal products. For three substances, none of the authorised products listed two or more manufacturing sites for the APIs and FPPs. This limited share of products with dual sourcing for APIs and FPPs and the overdependency on specific manufacturers were serious supply chain vulnerabilities observed in this study. 

#### Comparison with previous research

Studies on API and FPP manufacturers and their geographic locations have been limited. For the API market in general, we found data regarding the geographic distribution of manufacturers in relation to turnover according to suppliers. [18] Since the underlying numbers are lacking, the data are difficult to interpret. Recently, the European Commission published the results of the assessment of the supply chain vulnerabilities conducted in 2024 for a first tranche of 11 critical medicines from the Union list. [25] Using data collected from both EU member states and MAHs, several aspects were evaluated including diversification and geographic location of manufacturers. The risk thresholds/levels applied in this assessment (e.g. high risk with < 4 manufacturing sites), suggest that even more substances are at high risk compared to our findings. Similar to our study, this assessment found that MAHs were relatively less dependent on non-EU finished product manufacturers compared 

to their dependency on non-EU API manufacturers.

A recent study on generic APIs linked their manufacturing characteristics to medicine shortages in the U.S. [29]. This linkage provides an interesting possibility for further research.

#### **Strengths and limitations**

The major strength of our study is that we could analyse API as well as FPP manufacturing sites, the responsible MAHs, and their interdependencies. Our study showed that an analysis of 

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geographic location of only manufacturing sites is limited, since the geographic distribution of manufacturing sites differed from the geographic distribution of the sites for the medicinal products. Whereas 43% of the API manufacturing sites were located in Europe, 68% of the authorised medicinal products listed an API manufacturing site in Europe (36% in Europe only and 32% in Europe and another continent). For FPP manufacturing, 74% of the sites were in Europe and 84% of the authorised medicinal products listed a site in Europe. Larger differences were observed at the individual product level. Our analysis also yielded insights into the implementation of dual sourcing for over 400 authorised medicinal products.

Our study has three limitations. First, our cohort of ten high-use pharmaceutical substances out of over 13,000 (15) is unlikely to be representative of all medicines. For example, all of our substances are related to off-patent products. However, diverse supply chains were expected for high-use medicines because they are usually marketed by many MAHs. Also, the manufacturing of these off-patented medicines introduced complexity into the upstream supply chain due to increased outsourcing. (14) The overdependency on one and the same manufacturer, as observed for some substances in this study, is expected more often for other pharmaceutical substances, such as substances for niche medicines. For these ten substances, we also detected different patterns in the supply chains (isolated and intertwined supply chains), but we could not identify an overall sourcing strategy based on our data. Second, the included products were selected based on marketing authorisation in the Netherlands. Although MAHs may have different product portfolios in various countries, similar supply chain patterns are expected for products licenced in other countries in the EU or the European Economic Area (EEA), because most regulatory pathways in this region lead to authorisation in multiple member states or the entire EU or EEA. [36] Third, we focused only on API and FPP manufacturers and MAHs. Supply vulnerabilities can also be related to other factors, such as raw material and intermediate manufacturers, packaging sites, wholesalers, and distributors. The selected stakeholders are a crucial starting point, since they represent stringently regulated, core entities in the supply chain, and information on them could be extracted from a regulatory authority's database.

## Implications for policymakers and clinicians

Our granular analysis of the upstream pharmaceutical supply chains, displayed in Sankey diagrams, better facilitates the identification of supply chain vulnerabilities than numerical metrics. This facilitation will contribute to establishing effective measures to mitigate medicine shortages.

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This study provides transparency in the API and FPP manufacturing and related MAHs of ten high-use pharmaceuticals. Although the information on authorised medicinal products and related MAHs was readily available in the public database of medicine agencies, the specific manufacturing sites were not disclosed. Product-specific information regarding supply chains is closely guarded by the MAHs as trade secrets or confidential commercial information. [37, 38] Even though authorities have access to information on the specific manufacturing sites, this information is not necessarily available in a format enabling automated processing. [20] More transparency and standardised data on the supply chain, such as information on the APIs and FPPs that manufacturers prefer [39], would 

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allow for an improved analysis of vulnerabilities by MAHs or authorities. Various stakeholders have advocated the need for further transparency [17, 20]. 

The EU is conducting an analysis of the supply chains for medicines on the EU list of critical medicines to identify vulnerabilities and to determine how these can best be addressed. [24] However, supply chains for pharmaceutical substances not included on the current EU list of critical medicines, also showed vulnerabilities, such as strong dependency on one and the same FPP manufacturer (omeprazole) and manufacturing sites mainly located outside Europe (simvastatin). Policymakers should not overlook substances that are not indicated as critical at a regional or national level since supply interruptions for non-critical substances may also have a considerable societal impact due to the significant number of patients affected. Our study showed that the supply chains for these ten substances may be vulnerable due to the lack of dual sourcing, and overdependency on a specific manufacturer. 

In addition to transparency concerning API and FPP manufacturers and MAHs, an analysis of the relationship between supply chain vulnerabilities and the occurrence of medicine shortages in daily practice could provide further insights to help establish secure, resilient pharmaceutical supply chains.

#### CONCLUSION

Our study on the supply chains of high-use generic pharmaceutical substances identified the need for a granular assessment of the interdependencies between API and FPP manufacturers and MAHs to identify upstream supply chain vulnerabilities. 

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1 2		
2 3	361	ETHICS STATEMENTS
4 5	362	Ethics approval
6	363	Not required, since this study did not involve human subjects and therefore ethical approval was not
7 8	364	sought.
9	365	Consent for publication
10 11	366	Not applicable
12		
13 14	367	DATA AVAILABILITY STATEMENT
14	368	No additional data available, since data is related manufacturing locations of specific medicinal
16 17	369	products and manufacturers, which is confidential information.
17 18	370	Access to the internal database of the Dutch Medicines Evaluation Board (MEB) was granted to DJP
19	371	as part of her joint PhD trajectory with involvement of the MEB, Royal Dutch Pharmacists Association
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22	373	DJP. Data on individual authorised medicinal products, manufacturers and MAHs are published in a
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36 37	382	verified the study data. All authors contributed to the interpretation of the results. DJP and KN drafted
38	383	the manuscript and prepared tables and figures. All authors read and critically reviewed and
39 40	384	commented on each draft of the manuscript and approved the final manuscript for submission. DJP is
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42 43	386	and that no others meeting the criteria have been omitted.
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49 50	391	Competing interest statement
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52 53	392	All authors have completed the ICMJE uniform disclosure form at _and declare that the research was
53 54	392 393	All authors have completed the ICMJE uniform disclosure form at _and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a
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53 54 55 56 57 58	392 393 394 395 396	All authors have completed the ICMJE uniform disclosure form at _and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. <b>Disclaimer</b> The views expressed in this article are the personal views of the authors and must not be understood
53 54 55 56 57	392 393 394 395	All authors have completed the ICMJE uniform disclosure form at _and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Disclaimer

#### Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

#### Dissemination to participants and related patient and public communities

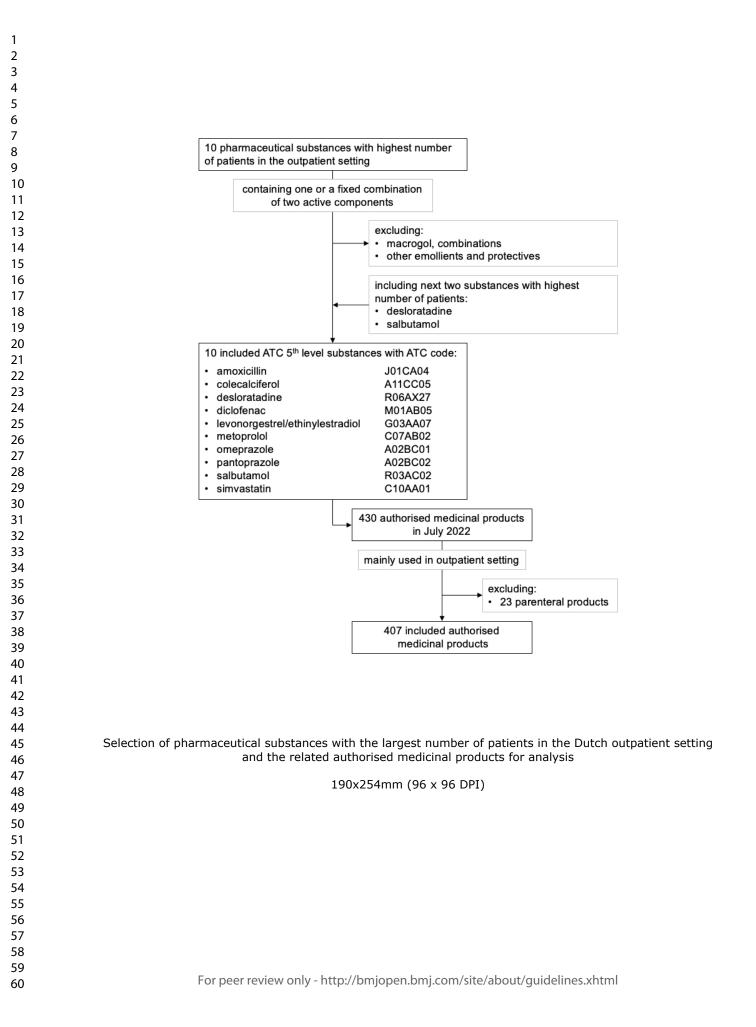
The authors plan to actively disseminate the study findings to the public and patients through social media and plain-language summaries on the websites of the authors' affiliated organisations. Also, the study findings will be forwarded to organisations participating in the national Working group on medicine shortages coordinated by the ministry of health, with representatives of all relevant hamaceu stakeholders such as pharmaceutical industry, health care professionals, patients and regulatory authorities. 

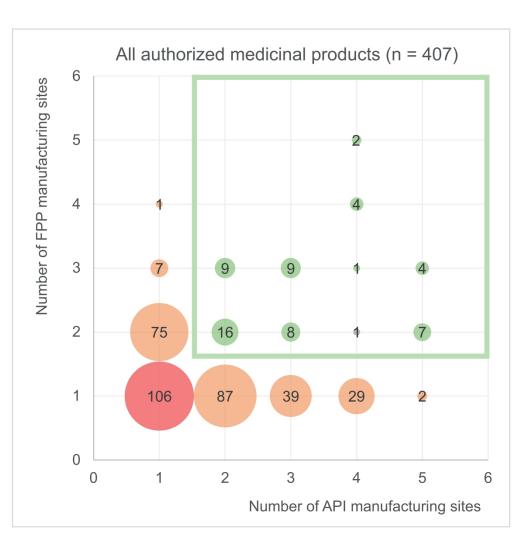
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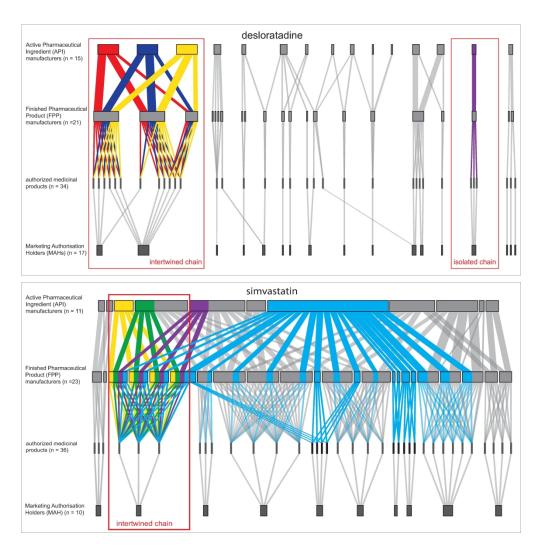


Number of authorised medicinal products with the corresponding number of manufacturing sites of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) according to the Dutch Medicines Evaluation Board database (n = 407).

Red = one manufacturing site for APIs and FPPs; orange = one manufacturing site for APIs or FPPs; green = at least two manufacturing sites for APIs and FPPs.

645x645mm (600 x 600 DPI)

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Exemplary supply chains for desloratadine (A) and simvastatin (B)

172x175mm (600 x 600 DPI)

## SUPPLEMENT TABLES AND FIGURES

### Supply chain vulnerabilities of high-use pharmaceuticals: an explorative cohort study

Doerine J Postma, Peter AGM De Smet, Aukje K Mantel-Teeuwisse, Hubert GM Leufkens, Kim Notenboom

**Table S1** – Overview of the included authorised medicinal products for outpatient use (n=407)

Table S2 - Authorised medicinal products relying on one (and the same) API or FPP manufacturer

**Figure S1** – Number of authorised medicinal products with a manufacturing site per country - active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP)\*

**Figure S2** – Number of manufacturing sites per authorised medicinal product - active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP)

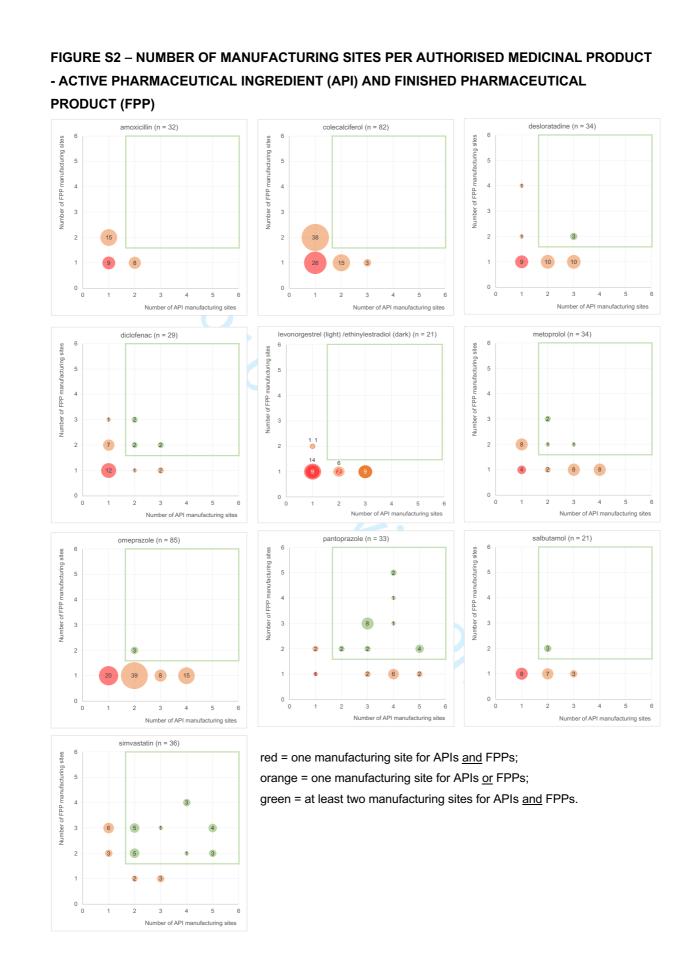
Figure S3 – Supply chains per pharmaceutical substance

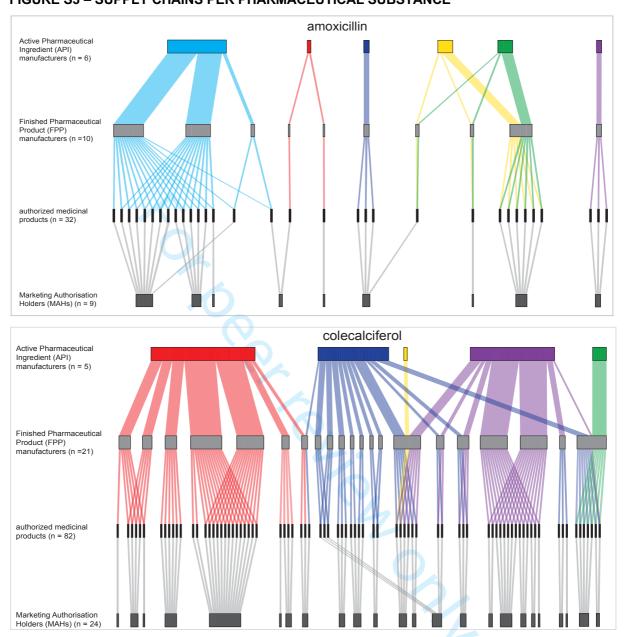
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## FIGURE S1 – NUMBER OF AUTHORISED MEDICINAL PRODUCTS WITH A MANUFACTURING SITE PER COUNTRY - ACTIVE PHARMACEUTICAL INGREDIENT (API) AND FINISHED PHARMACEUTICAL PRODUCT (FPP)\*

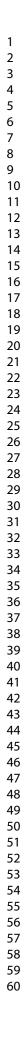


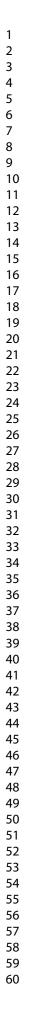
\* the sum of the products may be higher than the total number of products since a regulatory dossier for an authorised medicinal product may list manufacturers located in different countries

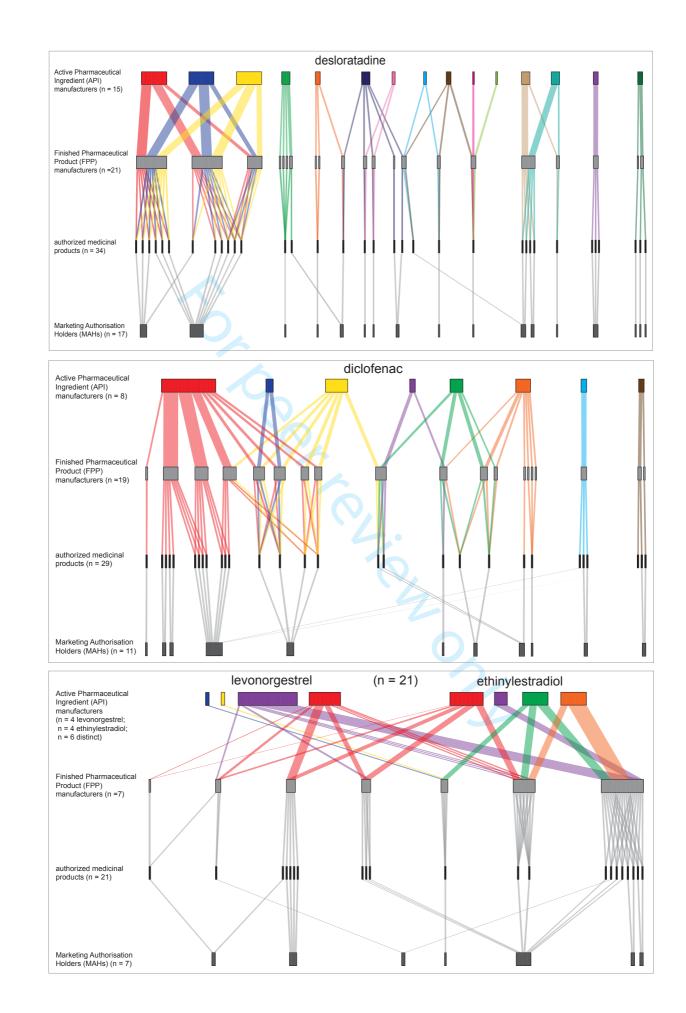


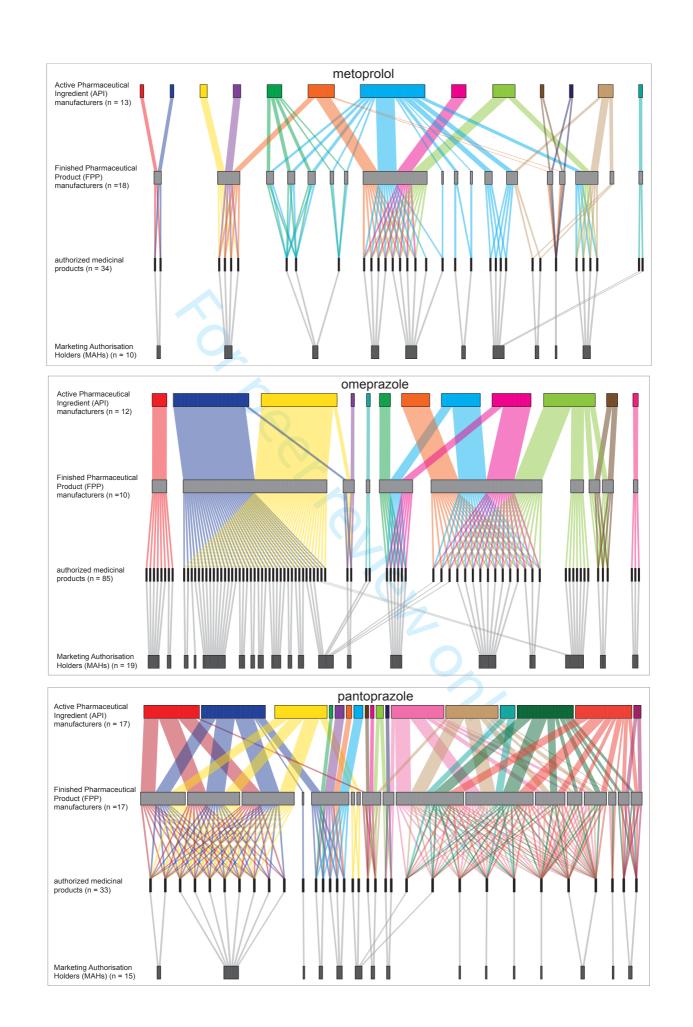


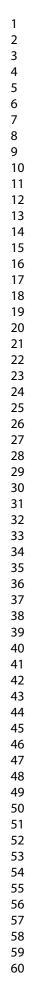
## FIGURE S3 – SUPPLY CHAINS PER PHARMACEUTICAL SUBSTANCE

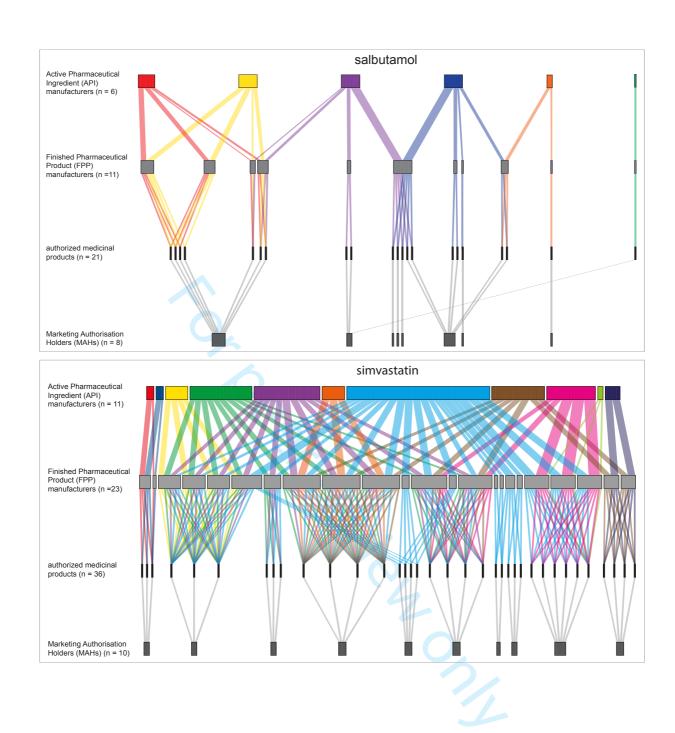












			number of patients (% of	patented or off- patent	Den by copyright, incluent of authorised medicinal proteses related to but total oral inhalated to but total oral oral oral oral oral oral oral or				number of marketing authorisation
			population)		total	oral	inhala 025	rectal	holders (MAHs)
amoxicillin J0	I01CA04	bacterial infection	815,000 (4.7)	off-patent	32	32	bow to t		
colecalciferol A	A11CC05	vitamin D deficiency	1,005,000 (5.8)	off-patent	82	82	ext p		
desloratadine R	R06AX27	allergy	740,000 (4.3)	off-patent	34	34	and		
diclofenac M	M01AB05	pain	815,000 (4.7)	off-patent	29	21	f fro ur ( <i>F</i> data	8	
levonorgestrel/ ethinylestradiol	G03AA07	contraception	1,000,000 (5.7)	off-patent	21	21	Downloaded from http://bmjopen.bmj.com/ pent Superieur (ABES) . 2 to text and data mining, Al training, and si		
metoprolol C	C07AB02	high blood pressure	1,010,000 (5.8)	off-patent	34	34	g, A		
omeprazole A	A02BC01	(prevention of) stomach ache	1,290,000 (7.4)	off-patent	85	85	l trai		
pantoprazole A	A02BC02	(prevention of) stomach ache	1,285,000 (7.4)	off-patent	33	33	en.b		
salbutamol R	R03AC02	asthma and COPD	780,000 (4.5)	off-patent	21		3, an <sup>2</sup> .		
simvastatin C	C10AA01	high cholesterol	845,000 (4.8)	off-patent	36	36	and sin		
Total			6,475,000* (37)		407	378	nilar 212	8	7(
,		patients is lower than the sum lower than the sum of the MA	of the number of	-	-	-	more theo	-	cal substance

## TABLE S2 – AUTHORISED MEDICINAL PRODUCTS RELYING ON ONE (AND THE SAME) API OR FPP MANUFACTURER

pharmaceutical	number of authorised medicinal products				
substance	total	one API manufacturer	one and the same API manufacturer		
amoxicillin	32	24 (75%)	16 (50%)		
colecalciferol	82	64 (78%)	34 (41%)		
desloratadine	34	11 (32%)	3 (9%)		
diclofenac	29	20 (69%)	12 (41%)		
levonorgestrel /	21	15 (71%)	7 (33%)		
ethinylestradiol	21	10 (48%)	10 (48%)		
metoprolol	34	12 (35%)	8 (24%)		
omeprazole	85	20 (24%)	8 (9%)		
pantoprazole	33	3 (9%)	2 (6%)		
salbutamol	21	8 (38%)	1 (5%)		
simvastatin	36	9 (25%)	9 (25%)		

## A. Active pharmaceutical ingredient (API) manufacturer

## B. Finished pharmaceutical product (FPP) manufacturer

pharmaceutical	number of authorised medicinal products				
substance	total	one FPP manufacturer	one and the same FPP manufacturer		
amoxicillin	32	17 (53%)	6 (19%)		
colecalciferol	82	44 (54%)	7 (9%)		
desloratadine	34	29 (85%)	6 (7%)		
diclofenac	29	15 (52%)	4 (14%)		
levonorgestrel /	21	20 (95%)	8 (38%)		
ethinylestradiol	21	20 (3370)	0 (00 %)		
metoprolol	34	22 (65%)	9 (26%)		
omeprazole	85	82 (86%)	39 (46%)		
pantoprazole	33	11 (31%)	5 (14%)		
salbutamol	21	18 (86%)	5 (24%)		
simvastatin	36	5 (31%)	3 (8%)		

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## Upstream pharmaceutical supply chains of ten high-use pharmaceuticals in the Netherlands: a cohort study

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<b>Primary Subject Heading</b> :	Health policy
Secondary Subject Heading:	Health policy, Public health
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, Pharmacists, Medicine

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Title	Upstream pharmaceutical supply chains of ten high-use
	pharmaceuticals in the Netherlands: a cohort study
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	253 7324

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3 4	2	UPSTREAM PHARMACEUTICAL SUPPLY CHAINS OF TEN HIGH-USE PHARMACEUTICALS IN
5	3	THE NETHERLANDS: A COHORT STUDY
6 7	4	
8	5	Doerine J Postma, <sup>1,2</sup> Peter AGM De Smet, <sup>3</sup> Aukje K Mantel-Teeuwisse,*1 Hubert GM Leufkens, <sup>1</sup> Kim
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17 18	13	4. Dutch Medicines Evaluation Board, Utrecht, the Netherlands
19	14	
20	15	*Corresponding author: Aukje K Mantel-Teeuwisse   Universiteitsweg 99, 3584 CG Utrecht, The Netherlands,
21 22	16	a.k.mantel@uu.nl, (0031)30 253 7324
23	17	ABSTRACT
24 25	17	<b>Objectives –</b> To assess the upstream pharmaceutical supply chains of ten high-use pharmaceuticals
26	18	
27 28	19	to detect vulnerabilities that may increase the risk of medicine shortages
28 29	20	Design – Cohort study
30	21	Setting – Dutch outpatient setting in 2022
31 32 33	22	Participants – A total of 407 authorised medicinal products for ten pharmaceutical substances with
	23	the largest number of outpatients
34	24	Main outcome measures – The diversity of active pharmaceutical ingredient (API) and finished
35 36	25	pharmaceutical product (FPP) manufacturers, their geographic locations and the interdependencies
37	26	between these manufacturers and marketing authorisation holders (MAHs)
38 39	27	Results – For the 407 authorised medicinal products, 50 of the 90 API manufacturing sites were in
40	28	Asia, and 38 in Europe. For five pharmaceutical substances, most of the API sites were located
41	29	outside Europe. Of the 128 FPP manufacturing sites, 94 were in Europe, and 31 in Asia. For all ten
42 43	30	substances, at least 47% of FPP sites were located in Europe.
44	31	API manufacturing for 122 of the 407 products (30%) was entirely performed outside Europe,
45 46	32	and FPP manufacturing for 66 of the 407 products (16%). For four substances, more than half of the
40 47	33	products depended on API manufacturing outside Europe.
48	34	The number of distinct API and FPP manufacturing sites per substance was at least four. For
49 50	35	amoxicillin, 16 of the 32 products (50%) entirely depended on one and the same API site. For
51	36	omeprazole, 39 of the 85 products (46%) entirely depended on one and the same FPP site.
52	37	MAHs applied dual sourcing for API and FPP manufacturing for 61 (15%) of the authorised
53 54	38	medicinal products. For three pharmaceutical substances, none of the authorised medicinal products
55	39	listed at least two API and FPP manufacturing sites.
56 57	40	<b>Conclusion</b> – Our study of the supply chains of high-use pharmaceutical substances indicates the
57 58	41	need for a granular assessment of the interdependencies between MAHs, API and FPP
59	42	manufacturers to identify upstream supply chain vulnerabilities.
60	74	

1 2		
3	43	STRENGTHS AND LIMITATIONS
4 5	44	- This study offers insights into the pharmaceutical supply chains, focussing on the diversity
6 7	45	of API and FPP manufacturers and their geographic locations.
8	46	- The use of Dutch Medicines Evaluation Board database to analyse the research question
9	47	is ideal since this is the official source to register this information.
10 11	48	- We visualised the ten upstream pharmaceutical supply chains using Sankey
12	49	diagrams, illustrating the complex interdependencies among stakeholders.
13 14	50	- Our cohort of ten pharmaceutical substances is unlikely to be representative of all
15	51	medicines.
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3	52	INTRODUCTION
4 5	53	A continuous supply of quality-assured, safe, effective, and affordable medicines is essential
6	54	for a well-functioning health system. [1] Until the beginning of the 21 <sup>st</sup> century the availability of
7 8	55	medicines did not significantly concern high-income countries. Then, discrepancies between supply
9	56	and demand began to frequently emerge. [2-4] Currently, medicine shortages are 'the new normal'. [5,
10 11	57	6] The main causes of medicine shortages are related to manufacturing and quality issues [7, 8],
12	58	which are part of the upstream supply chain, from active pharmaceutical ingredient (API) to FPP
13	59	manufacturing and packaging, rather than the downstream distribution. [9] Despite the increased focus
14 15	60	on the availability of medicines during the COVID-19 pandemic, shortages further increased post-
16	61	COVID-19, [10-12] underscoring the necessity of addressing the ongoing challenges in the
17 18	62	pharmaceutical supply chain.
19	63	The pharmaceutical supply chain is complex, involving multiple interdependent stakeholders
20 21	64	and relying on a global distribution network. MAHs are responsible for their authorised medicinal
21	65	products and for the qualification and selection of the involved (number of) manufacturers. MAHs often
23	66	rely on manufacturers located worldwide to produce APIs and finished pharmaceutical products
24 25	67	(FPPs). [13] MAHs may decide to manufacture APIs and FPPs in-house, which offers control over
26	68	quality, quantity, and timelines, thus providing the flexibility to rapidly respond to manufacturing
27 28	69	problems requiring expertise and resources. However, manufacturing generic products is increasingly
29	70	outsourced, enlarging external dependency and introducing complexity into the upstream supply
30 31	71	chain. [14] A much-raised additional concern is the geographical location and concentration of
32	72	manufacturing sites, particularly in Asia. [15-17] Studies on manufacturing sites and their geographic
33	73	locations are limited. For the API market in general, we found data regarding the geographic
34 35	74	distribution of manufacturers in relation to turnover. According to the researchers, API manufacturing
36	75	for the European market is predominantly situated in Asia (56%), followed by Western Europe (24%)
37 38	76	and North America (12%), with limited contributions from the rest of the world (8%). [18]
39	77	The supply chain may be disturbed by manufacturing issues, natural disasters, or geopolitical
40 41	78	disputes. Problems with API availability may disrupt FPP manufacturing, impact the marketing of
42	79	authorised medicinal products by MAHs, prohibit dispensing by the pharmacist, and ultimately restrict
43 44	80	patient access. A robust supply chain would prevent a problem occurring at one point in the supply
44	81	from causing disruptions elsewhere. To enhance supply chain resilience, ensuring supplier diversity is
46	82	considered crucial. [19, 20] For a viable market, a supplier base of at least three different API and FPP
47 48	83	manufacturers per pharmaceutical substance is considered desirable according to participants at a
49	84	WHO-convened technical consultation. [21] Dual sourcing strategies per authorised medicinal product
50 51	85	- establishing two suppliers for a given ingredient or component in a regulatory product dossier - is
52	86	also a well-known measure. [20, 22]
53 54	87	Supply chain resilience is in the spotlight of global pharmaceutical policies. [17, 23] The
55	88	European Commission is analysing supply chains of medicines on the EU list of critical medicines to
56	89	identify vulnerabilities. Foreseen EU policy measures to strengthen these supply chains include
57 58	90	regulatory flexibilities and recommendations to diversify manufacturers and increase Europe's
59	91	manufacturing capacity. [24-26] Insight into interdependencies among stakeholders – such as the
60		

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number of API manufacturers supplying FPP manufacturers and the subsequent number of FPP manufacturers supplying different MAHs, along with their geographic locations - can help to identify supply chain vulnerabilities. Although geographic concentration is often reported as an issue, and medicine shortages and pharmaceutical supply chain vulnerabilities have been linked by some researchers [27-30], no studies have specifically analysed the interdependencies among stakeholders in the upstream pharmaceutical supply chain. There is currently also no method that could be translated into public health resilience planning. 

This research aimed to assess pharmaceutical supply chains by evaluating the diversity of API and FPP manufacturers, their geographic locations and the interdependencies between MAHs and these manufacturers. We selected ten pharmaceutical substances with the largest number of Inds sin. outpatients in the Netherlands since supply disruptions of these medicines may affect a significant share of the population.

2		
3 4	104	METHODS
5	105	Study population and data collection
6 7	106	For this cohort study, ten pharmaceutical substances with the largest number of patients in the
8	107	Dutch outpatient setting were chosen because the number of patients is a key element determining a
9	108	shortage's impact. [31] As a result of choosing the number of patients (instead of for example the total
10 11	109	annual volume) all treatments were counted equally, regardless of treatment duration. The ten high-
12	110	use pharmaceutical substances in 2021 originated from the database of the Dutch Foundation for
13 14	111	Pharmaceutical Statistics [32, 33], which contains complete information on the Dutch outpatient setting
15	112	including the outpatient pharmacies in hospitals. The pharmaceutical substances were classified
16	113	according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system, which
17 18	114	classifies active pharmaceutical substances into five hierarchical levels according to the organ or
19	115	system on which they act and their therapeutic, pharmacological and chemical properties. ATC on the
20 21	116	fifth level indicates the active substance, also known as API. [34] We included pharmaceutical
22	117	substances containing one or a fixed combination of two active components.
23 24	118	The medicinal products containing these ten pharmaceutical substances authorised in the
25	119	Netherlands, along with their responsible MAHs and the involved API and FPP manufacturers and
26	120	their geographic locations, were identified using the Dutch Medicines Evaluation Board (MEB) [35]
27 28	121	database in July 2022. We excluded products for parenteral use such as solution for injection or
29	122	infusion. These products are mainly prescribed in hospital settings and therefore not included in the
30 31	123	data from the Dutch Foundation for Pharmaceutical Statistics.
32	124	Study outcomes and data analysis
33 34	125	For the authorised medicinal products, a researcher (DJP) obtained distinct MAHs, API and
35	126	FPP manufacturers, and geographic locations of the manufacturers at the country and continent
36 37	127	levels. The geographic locations were limited to API and FPP manufacturing sites because they are
38	128	more geographically bound than MAHs, and regulatory requirements are involved when changing
39 40	129	1
40 41		them. [36]
- 1	130	them. [36] We calculated the median number of authorised medicinal products per MAH and the
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42 43		We calculated the median number of authorised medicinal products per MAH and the
42 43 44 45	131	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API
42 43 44 45 46	131 132	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical
42 43 44 45 46 47 48	131 132 133	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical substances, we only plotted the manufacturers of the substances with the fewest API manufacturers
42 43 44 45 46 47 48 49	131 132 133 134	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical substances, we only plotted the manufacturers of the substances with the fewest API manufacturers because it represented the worst case and, thus, greatest overall vulnerability.
42 43 44 45 46 47 48	131 132 133 134 135	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical substances, we only plotted the manufacturers of the substances with the fewest API manufacturers because it represented the worst case and, thus, greatest overall vulnerability. We mapped the pharmaceutical supply chains using Sankey diagrams containing nodes and
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42 43 44 45 46 47 48 49 50 51 52 53	131 132 133 134 135 136 137	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical substances, we only plotted the manufacturers of the substances with the fewest API manufacturers because it represented the worst case and, thus, greatest overall vulnerability. We mapped the pharmaceutical supply chains using Sankey diagrams containing nodes and links to visualise stakeholder interdependencies. The nodes represent the API manufacturer, the FPP manufacturer, authorised medicinal products, and the MAH, respectively. The links show their
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42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	131 132 133 134 135 136 137 138 139	We calculated the median number of authorised medicinal products per MAH and the interquartile range (IQR) and range. For authorised medicinal products, we plotted the number of API versus FPP manufacturing sites on a bubble chart. For products containing two pharmaceutical substances, we only plotted the manufacturers of the substances with the fewest API manufacturers because it represented the worst case and, thus, greatest overall vulnerability. We mapped the pharmaceutical supply chains using Sankey diagrams containing nodes and links to visualise stakeholder interdependencies. The nodes represent the API manufacturer, the FPP manufacturer, authorised medicinal products, and the MAH, respectively. The links show their interactions. The width of the nodes is proportional to the number of links; a wider node means more interaction with next-stage stakeholders.
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2 3	143	Patient and Public Involvement
4 5	144	Neither patients nor the public were involved in the conception, design, or execution of this study.
6 7	145	ETHICS STATEMENTS
8	146	Ethics approval
9 10	147	Ethics approval was not required according to Dutch law, since this study did not involve human
10	148	subjects.
12	149	Consent for publication
13 14	150	-
15	151	Not applicable
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2 3	152	RESULTS
4	153	The ten pharmaceutical substances with the largest number of patients in the outpatient
5 6	154	setting in the Netherlands included two ATC fifth-level substances containing more than two active
7	155	components. These two substances were replaced by the next two ATC fifth-level substances that met
8 9	156	the inclusion criteria. For the selected substances, 407 medicinal products for outpatient use were
9 10	150	authorised in the Netherlands in July 2022 (Figure 1). In total, 37% of the Dutch population (6.5 million
11	158	people) received a prescription for one or more of the selected medicinal products (see supplementary
12 13	159	table S1).
14	160	
15 16	161	Figure 1: Selection of pharmaceutical substances with the largest number of patients in the Dutch
17	162	outpatient setting and the related authorised medicinal products for analysis
18 19	163	
20	164	The 407 products included authorised off-patent medicinal products predominantly intended
21	165	for oral use (378; 93%), with a few for inhalation (21; 5%) or rectal use (8; 2%). The number of
22 23	166	authorised medicinal products per pharmaceutical substance ranged from 21 for
24	167	levonorgestrel/ethinylestradiol and salbutamol to 85 products for omeprazole. The 407 authorised
25 26	168	medicinal products were the responsibility of 70 distinct MAHs (see supplementary table S1), and their
27	169	manufacturing involved 90 distinct API sites and 128 distinct FPP sites. Three manufacturing sites
28 29	170	produced APIs as well as FPPs. In our cohort of 407 products, the 70 MAHs were responsible for a
30	171	median of three (IQR: 2–6) authorised medicinal products (range: 1–42). Of the 70 MAHs, 49 had
31 32	172	marketing authorisations for products for one of the ten pharmaceutical substances. Three MAHs had
33	173	marketing authorisations for products for nine of the ten pharmaceutical substances.
34 35	174	
35 36	175	API manufacturing
37	176	The 90 API manufacturers for the 407 authorised medicinal products were mostly located in
38 39	177	Asia (50; 55%), a large minority in Europe (38; 42%), and rarely in the Americas (2; 3%) (see Table 1
40	178	and supplementary figure S1). The number of distinct API manufacturing sites per pharmaceutical
41 42	179	substance ranged from four for levonorgestrel/ethinylestradiol to 17 for pantoprazole. For
43	180	desloratadine, diclofenac, metoprolol, pantoprazole, and simvastatin, more than half of the API
44 45	181	manufacturing sites were located outside Europe (54%–82%). For amoxicillin and omeprazole, the
46	182	API sites were equally divided outside and within Europe. For the remaining three substances, a
47 48	183	minority of the sites were located outside Europe (range: 0%–40%) thus for the majority within Europe
40	184	(60–100%). For all pharmaceutical substances at least two API manufacturing sites were located in
50	185	Europe.
51 52	186	Among the 407 authorised medicinal products, 122 entirely relied on APIs manufactured
53	187	outside of Europe (Table 1). For four substances (desloratadine, diclofenac, pantoprazole, and
54 55	188	simvastatin), the authorised medicinal products predominantly relied on only API manufacturing sites
56	189	outside of Europe (range: 52–66%). For colecalciferol, metoprolol and omeprazole, the API
57 58	190	manufacturing sites were outside and within Europe. For the remaining three substances, the minority
59	191	of the products relied on API sites outside Europe (range: 0–25%). The number of authorised
60		

8 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 192 medicinal products per substance specified per country of the manufacturing site is displayed in

193 supplementary figure S1.

Table 1: Number and geographic location (continent) of active pharmaceutical ingredient (API)
 manufacturing sites and related medicinal products

# manufacturing sites and related medicinal products number of API manufacturing number of related authorised medicinal sites per continent products per continent

	num	sites per cont	•	number of related authorised medicinal products per continent				
pharmaceutical substance	total	Europe	other continents	total	Europe	Europe and other continents*	other continents	
overall	90	38 (42%)	52 (58%)	407	146 (36%)	139 (34%)	122 (30%)	
amoxicillin	6	3 (50%)	3 (50%)	32	24 (75%)		8 (25%)	
colecalciferol	5	3 (60%)	2 (40%)	82	47 (57%)	18 (22%)	17 (21%)	
desloratadine	15	3 (20%)	12 (80%)	34		15 (44%)	19 (56%)	
diclofenac	8	3 (38%)	5 (62%)	29	7 (24%)	3 (10%)	19 (66%)	
levonorgestrel / ethinylestradiol	4 4	4 (100%) 4 (100%)		21	21 (100%)			
metoprolol	13	6 (46%)	7 (54%)	34	13 (38%)	16 (47%)	5 (15%)	
omeprazole	12	6 (50%)	6 (50%)	85	14 (16%)	56 (66%)	15 (18%)	
pantoprazole	17	4 (24%)	13 (76%)	33		16 (48%)	17 (52%)	
salbutamol	6	5 (83%)	1 (17%)	21	20 (95%)		1 (5%)	
simvastatin	11	2 (18%)	9 (82%)	36		15 (42%)	21 (58%)	

\* The regulatory dossier for an authorised medicinal product may list several API manufacturers on different continents.

#### FPP manufacturing

The 128 FPP manufacturing sites for the 407 authorised medicinal products were mainly situated in Europe (94; 74%), to a lesser extent in Asia (31; 24%), and rarely in the Americas (3; 2%) (see Table 2 and supplementary figure S1). The number of distinct FPP manufacturing sites per pharmaceutical substance ranged from seven for levonorgestrel/ethinylestradiol to 23 for simvastatin. For pantoprazole a small majority (53%) of FPP sites were located outside Europe and for amoxicillin the FPP sites were equally divided outside and within Europe. For the other eight substances, the minority of FPP sites were located outside Europe (range: 0-48%). For all ten pharmaceutical substances at least five FPP manufacturing sites were present in Europe.

Of the related authorised medicinal products, 66 of the 407 (16%) were entirely manufactured outside Europe (Table 2). For all substances, the minority of the authorised medicinal products relied solely on FPP manufacturing outside Europe (range: 0–38%). The number of authorised medicinal products per substance specified per country of the manufacturing site is displayed in supplementary figure S1.

## Table 2: Number and geographic location (continent) of finished pharmaceutical product (FPP) manufacturing sites and related medicinal products

pharmaceutical		er of FPP mai sites per cont	-	Number of related authorised medicinal products per continent			
substance	Total	Europe	other continents	total	Europe	Europe and other continents*	other continents
overall	128	94 (73%)	34 (17%)	407	286 (70%)	55 (14%)	66 (16%)

amoxicillin	10	5 (50%)	5 (50%)	32	23 (72%)		9 (28%)
colecalciferol	21	17 (81%)	4 (19%)	82	56 (68%)	14 (17%)	12 (15%)
desloratadine	21	15 (71%)	6 (29%)	34	20 (59%)	1 (3%)	13 (38%)
diclofenac	19	16 (84%)	3 (16%)	29	24 (83%)	3 (10%)	2 (7%)
levonorgestrel/ ethinylestradiol	7	6 (86%)	1 (14%)	21	18 (86%)		3 (14%)
metoprolol	18	14 (78%)	4 (22%)	34	25 (74%)	5 (15%)	4 (12%)
omeprazole	10	7 (70%)	3 (30%)	85	77 (91%)	3 (3%)	5 (6%)
pantoprazole	17	8 (47%)	9 (53%)	33	14 (42%)	14 (42%)	5 (16%)
salbutamol	11	11 (100%)		21	21 (100%)		
simvastatin	23	12 (52%)	11 (48%)	36	8 (22%)	15 (42%)	13 (36%)
* The regulatory dossie	r for an a	, ,	inal product may	/ list sever	al FPP manufac	turers on differen	. ,

#### 218 Diversity of manufacturers

The regulatory dossiers of 346 of the 407 products (85%) listed either one API manufacturing and multiple FPP sites (83; 20%), one FPP manufacturing and multiple API sites (157; 39%), or one API and one FPP site (106; 26%) (Figure 2). For 61 authorised medicinal products (15%), at least two API and FPP sites were listed. For four substances, most authorised medicinal products (69%-78%) relied on one API manufacturing site. For eight substances, more than half of the authorised medicinal products (52%–95%) relied on one FPP manufacturing site (see supplementary table S2). For amoxicillin, colecalciferol, and levonorgestrel/ethinylestradiol, none of the authorised products listed two or more manufacturing sites for the APIs and FPPs (see supplementary figure S2). For simvastatin and pantoprazole, most of the authorised medicinal products (both 61%) listed at least two manufacturing sites for the APIs and FPPs.

# Figure 2: Number of authorised medicinal products with the corresponding number of manufacturing sites of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) according to the Dutch Medicines Evaluation Board database (n = 407).

Red = one manufacturing site for APIs <u>and</u> FPPs; orange = one manufacturing site for APIs <u>or</u> FPPs; green = at
least two manufacturing sites for APIs <u>and</u> FPPs.

#### 236 Interdependency

The flow of the ten upstream pharmaceutical supply chains is illustrated in Sankey diagrams showing the journey from API manufacturer to FPP manufacturer, ending in an authorised medicinal product under the responsibility of an MAH (see supplementary figure S3). We identified two main patterns of supply chains, the 'isolated chain' and the 'intertwined chain', for example, as depicted in the diagrams of desloratadine (Figure 3A) and simvastatin (Figure 3B), respectively. The isolated chain involves (in extremis) one MAH depending on one API and one FPP manufacturer. The intertwined chain consists of multiple API and FPP manufacturers serving multiple MAHs. Of the 70 distinct MAHs, 11 (16%) depended on one API manufacturer and one FPP site

54244Of the 70 distinct MAHs, 11 (16%) depended on one API manufacturer and one FPP site5556245(isolated chain), 14 (20%) on one API manufacturer and multiple FPP sites, 20 (28%) on multiple API57246sites and one FPP manufacturer, and 25 (36%) on multiple API and FPP sites (intertwined chain).58247When an MAH relied on several manufacturers, the same combinations of API and FPP60248manufacturers (intertwined chain, Figure 3A and B) occurred.

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1 2		
3	249	Simvastatin was remarkable because 29 of the 36 (81%) authorised medicinal products listed
4 5	250	the same API manufacturer (Figure 3B; light blue). Upon closer examination, only nine of these
5 6	251	products (25%) entirely depended on this manufacturer. A further analysis of the manufacturer
7	252	dependencies for all substances showed that amoxicillin was notable for 50% of authorised products
8 9	253	relying on one and the same API manufacturer, and omeprazole was notable for 46% of authorised
10	254	products relying on one and the same FPP manufacturer (see supplementary table S2).
11 12	255	
13	256	Figure 3: Exemplary supply chains for desloratadine (A) and simvastatin (B)
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2		
3	257	DISCUSSION
4 5	258	Principal findings
6	259	This study on the upstream pharmaceutical supply chains of ten high-use pharmaceuticals unravelled
7 8	260	several overall existing concerns. For these substances, a significant proportion of the API and FPP
9	261	manufacturing sites were located in Europe, and an even higher proportion of the related authorised
10 11	262	medicinal products listed an API or FPP manufacturing site in Europe. All ten substances had a
12	263	supplier base exceeding at least three different API and FPP manufacturers, which is desirable for a
13 14	264	viable market [21]. Dual sourcing for API and FPP manufacturing, however, was present for a minority
15	265	of the authorised medicinal products.
16 17	266	The dependency on API and FPP manufacturing sites in Asia [15, 16] was less pronounced
17 18	267	than expected. For the ten substances, 43% and 74% of the API and FPP manufacturing sites,
19	268	respectively, were located in Europe and were involved in the manufacturing of 68% and 84% of the
20 21	269	related authorised medicinal products, respectively. However, for four pharmaceutical substances,
22	270	more than half of the products (54–67%) did rely on non-European API manufacturers. For each
23 24	271	pharmaceutical substance, at least four different API and seven different FPP manufacturers were
25	272	listed, thus exceeding an supplier base of at least three manufacturers for APIs and FPPs. [21]
26 27	273	Nevertheless, some substances were overdependent on one and the same manufacturer, such as
27	274	amoxicillin (strongly depending on one and the same API manufacturer) and omeprazole (strongly
29	275	depending on one and the same FPP manufacturer). MAHs had adopted a dual sourcing strategy for
30 31	276	API and FPP manufacturing for only 15% of the authorised medicinal products. For three substances,
32	277	none of the authorised products listed two or more manufacturing sites for the APIs and FPPs. This
33 34	278	limited share of products with dual sourcing for APIs and FPPs and the overdependency on specific
35	279	manufacturers were serious supply chain vulnerabilities observed in this study.
36 37	280	Comparison with previous research
38	281	Studies on API and FPP manufacturers and their geographic locations have been limited. For
39 40	282	the API market in general, we found data regarding the geographic distribution of manufacturers in
41	283	relation to turnover according to suppliers. [18] Since the underlying numbers are lacking, the data are
42 43	284	difficult to interpret. Recently, the European Commission published the results of the assessment of
44	285	the supply chain vulnerabilities conducted in 2024 for a first tranche of 11 critical medicines from the
45	286	Union list. [25] Using data collected from both EU member states and MAHs, several aspects were
46 47	287	evaluated including diversification and geographic location of manufacturers. The risk
48	288	thresholds/levels applied in this assessment (e.g. high risk with < 4 manufacturing sites), suggest that
49 50	289	even more substances are at high risk compared to our findings. Similar to our study, this assessment
51	290	found that MAHs were relatively less dependent on non-EU finished product manufacturers compared
52 53	291	to their dependency on non-EU API manufacturers.
54	292	A recent study on generic APIs linked their manufacturing characteristics to medicine
55 56	293	shortages in the U.S. [30]. This linkage provides an interesting possibility for further research.
57	294	Strengths and limitations
58 50	295	The major strength of our study is that we could analyse API as well as FPP manufacturing
59 60	296	sites, the responsible MAHs, and their interdependencies. Our study showed that an analysis of

geographic location of only manufacturing sites is limited, since the geographic distribution of manufacturing sites differed from the geographic distribution of the sites for the medicinal products. Whereas 43% of the API manufacturing sites were located in Europe, 68% of the authorised medicinal products listed an API manufacturing site in Europe (36% in Europe only and 32% in Europe and another continent). For FPP manufacturing, 74% of the sites were in Europe and 84% of the authorised medicinal products listed a site in Europe. Larger differences were observed at the individual product level. Our analysis also yielded insights into the implementation of dual sourcing for over 400 authorised medicinal products. Our study has three limitations. First, our cohort of ten high-use pharmaceutical substances out of over 13,000 [20] is unlikely to be representative of all medicines. For example, all of our substances are related to off-patent products. However, diverse supply chains were expected for high-

use medicines because they are usually marketed by many MAHs. Also, the manufacturing of these off-patented medicines introduced complexity into the upstream supply chain due to increased outsourcing. [37] As these off-patent medicines are often expected to have a relatively robust supply chain, our approach highlights the minimum risks that the supply chain may face. The overdependency on one and the same manufacturer, as observed for some substances in this study, is expected more often for other pharmaceutical substances, such as substances for niche medicines. For these low-use pharmaceutical substances, dual-sourcing may not always be possible, e.g. because of a single supplier, or be particularly costly considering the small scale of production. [20, 26] For the ten substances in the present study, we also detected different patterns in the supply chains (isolated and intertwined supply chains), but we could not identify an overall sourcing strategy based on our data. Second, the included products were selected based on marketing authorisation in the Netherlands. Although MAHs may have different product portfolios in various countries, similar supply chain patterns are expected for products licenced in other countries in the EU or the European Economic Area (EEA), because most regulatory pathways in this region lead to authorisation in multiple member states or the entire EU or EEA. [38] Third, we focused only on API and FPP manufacturers and MAHs. Supply vulnerabilities can also be related to other factors, such as raw material and intermediate manufacturers, packaging sites, wholesalers, and distributors. The selected stakeholders are a crucial starting point, since they represent stringently regulated, core entities in the supply chain, and information on them could be extracted from a regulatory authority's database. 

46<br/>47327Implications for policymakers and clinicians

Our granular analysis of the upstream pharmaceutical supply chains, displayed in Sankey
 diagrams, better facilitates the identification of supply chain vulnerabilities than numerical metrics. This
 facilitation will contribute to establishing effective measures to mitigate medicine shortages.

This study provides transparency in the API and FPP manufacturing and related MAHs of ten high-use pharmaceuticals. Although the information on authorised medicinal products and related MAHs was readily available in the public database of medicine agencies, the specific manufacturing sites were not disclosed. Product-specific information regarding supply chains is closely guarded by the MAHs as trade secrets or confidential commercial information. [39, 40] Even though authorities have access to information on the specific manufacturing sites, this information is not necessarily 

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available in a format enabling automated processing. [20] More transparency and standardised data	
on the supply chain, such as information on the APIs and FPPs that manufacturers prefer [41], would	
allow for an improved analysis of vulnerabilities by MAHs or authorities. Various stakeholders have	-
advocated the need for further transparency [17, 20].	
The EU is conducting an analysis of the supply chains for medicines on the EU list of critical	
medicines to identify vulnerabilities and to determine how these can best be addressed. [24] However,	-
supply chains for pharmaceutical substances not included on the current EU list of critical medicines,	
also showed vulnerabilities, such as strong dependency on one and the same FPP manufacturer	
(omeprazole) and manufacturing sites mainly located outside Europe (simvastatin). Policymakers	Prot
should not overlook substances that are not indicated as critical at a regional or national level since	ecte
supply interruptions for non-critical substances may also have a considerable societal impact due to	d by
the significant number of patients affected. Our study showed that the supply chains for these ten	Cop
substances may be vulnerable due to the lack of dual sourcing, and overdependency on a specific	oyrig
manufacturer.	yht, i
We acknowledged that our cohort consisted of only ten pharmaceutical substances. Larger	nclu
and more systematically differentiated samples (such as substances with established supply	Idin
shortages) may yield different findings. We encourage future researchers to investigate this topic for	g foi
complementary insights.	Г. <u>П</u> .
In addition to transparency concerning API and FPP manufacturers and MAHs, an analysis of	Enseigneme Protected by copyright, including for uses related t
the relationship between supply chain vulnerabilities and the occurrence of medicine shortages in daily	gner late
practice could provide further insights to help establish secure, resilient pharmaceutical supply chains.	dt

#### CONCLUSION

Our study on the supply chains of high-use generic pharmaceutical substances identified the need for a granular assessment of the interdependencies between API and FPP manufacturers and MAHs to identify upstream supply chain vulnerabilities. Policymakers should direct and amend their policies to effective measures to mitigate medicine shortages. They may also need to acquire a better understanding of the supply chains and its resilience. To aid, the method used in this study could be translated into a tool for public health resilience planning. 

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2							
3	365	DATA AVAILABILITY STATEMENT					
4 5	366	No additional data available, since data is related manufacturing locations of specific medicinal					
6	367	products and manufacturers, which is confidential information.					
7 8	368	Access to the internal database of the Dutch Medicines Evaluation Board (MEB) was granted to DJP					
9	369	as part of her joint PhD trajectory with involvement of the MEB, Royal Dutch Pharmacists Association					
10	370	(KNMP) and University Utrecht. Conflict of interest and a confidentiality agreement was signed by					
11 12	371	DJP. Data on individual authorised medicinal products, manufacturers and MAHs are published in a					
13	372	de-identified manner. The manuscript was checked by the legal department of the MEB for					
14 15	373	confidential information prior to publishing.					
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30	382	commented on each draft of the manuscript and approved the final manuscript for submission. DJP is					
31 32 33 34	383	the study guarantor. The corresponding author attests that all listed authors meet authorship criteria					
	384	and that no others meeting the criteria have been omitted.					
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42 43	391	Competing interests       None declared       Disclaimer					
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45 46	393	The views expressed in this article are the personal views of the authors and must not be understood					
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48 49	394	Board or the Royal Dutch Pharmacists Association.					
49 50	395	Transparency					
51	396	The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and					
52 53	397	transparent account of the study being reported; that no important aspects of the study have been					
54	398	omitted; and that any discrepancies from the study as planned (and if relevant, registered) have been					
55 56	399	explained.					
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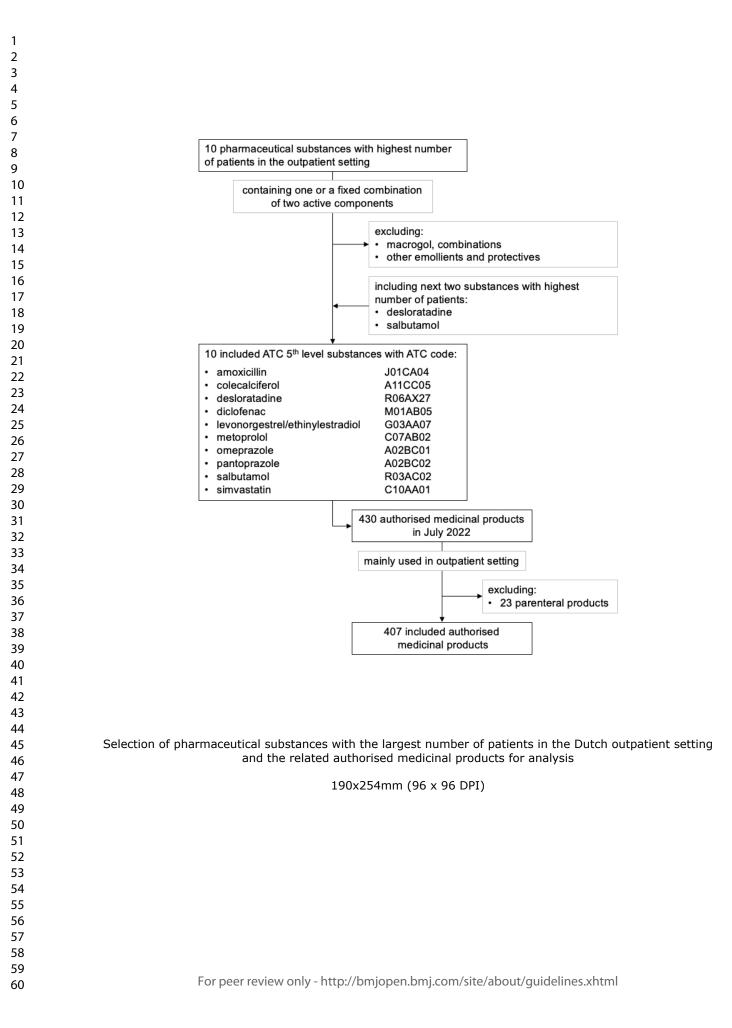
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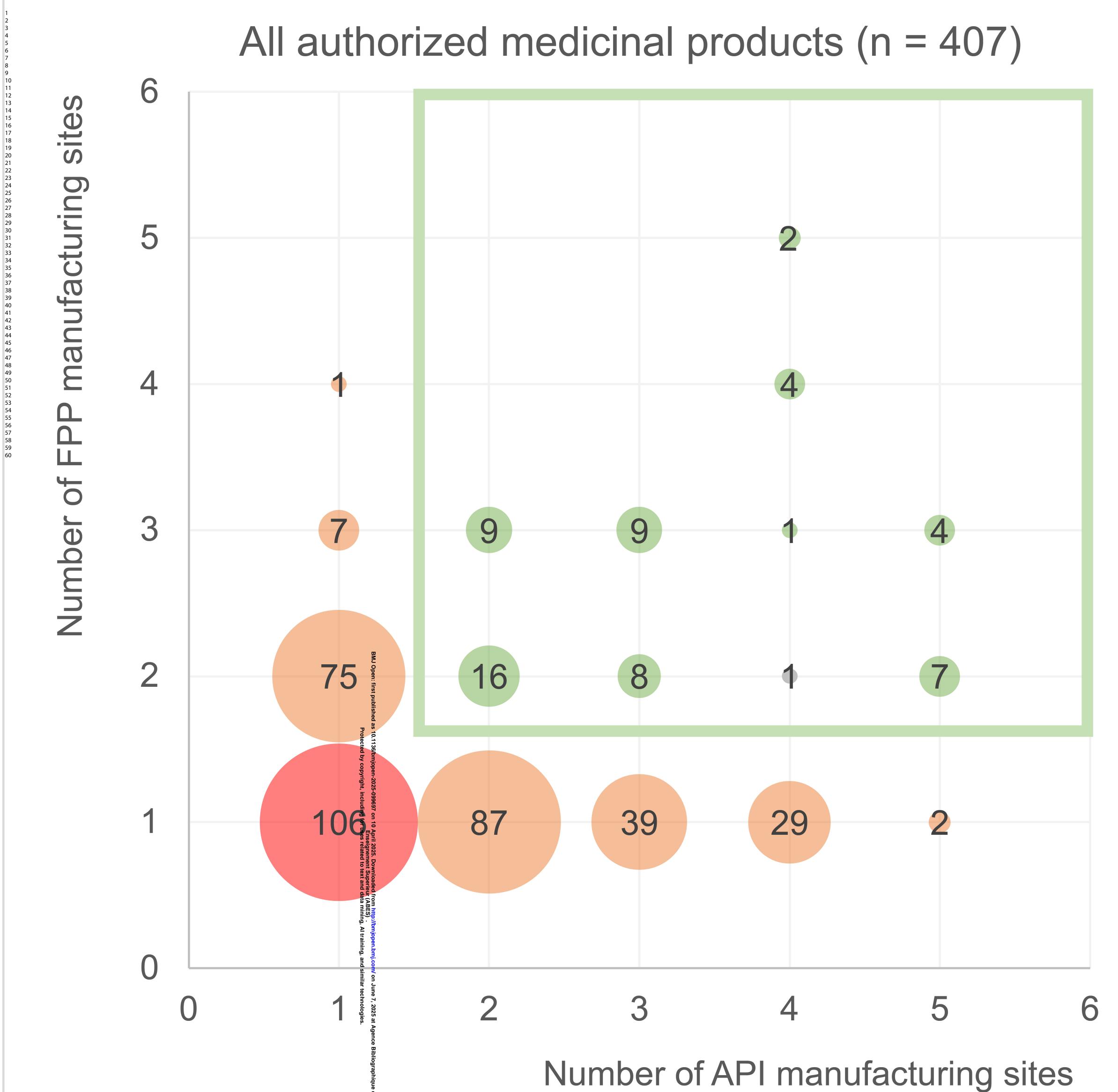
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51	532	FIGURE LEGENDS
52	533	Figure 1: Selection of pharmaceutical substances with the largest number of patients in the Dutch outpatient
53	534	setting and the related authorised medicinal products for analysis
54 55	535	Figure 2: Number of authorised medicinal products with the corresponding number of manufacturing sites of
55 56	536	active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) according to the Dutch
57	537	Medicines Evaluation Board database ( $n = 407$ ).
58	538	Red = one manufacturing site for APIs and FPPs; orange = one manufacturing site for APIs or FPPs; green = at
59	539	least two manufacturing sites for APIs and FPPs.
60	003	icast two manulactuling sites for AL is and FFFS.

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3	540	Figure 3: Exemplary supply chains for desloratadine (A) and simvastatin (B)
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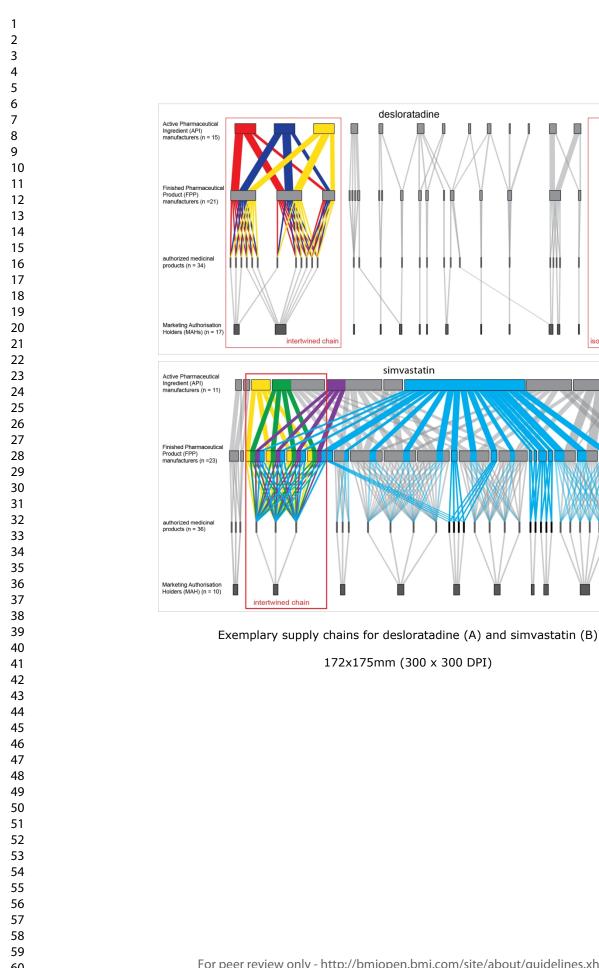
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#### SUPPLEMENT TABLES AND FIGURES

#### Supply chain vulnerabilities of high-use pharmaceuticals: an explorative cohort study

Doerine J Postma, Peter AGM De Smet, Aukje K Mantel-Teeuwisse, Hubert GM Leufkens, Kim Notenboom

**Table S1** – Overview of the included authorised medicinal products for outpatient use (n=407)

Table S2 - Authorised medicinal products relying on one (and the same) API or FPP manufacturer

**Figure S1** – Number of authorised medicinal products with a manufacturing site per country - active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP)\*

**Figure S2** – Number of manufacturing sites per authorised medicinal product - active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP)

Figure S3 – Supply chains per pharmaceutical substance

### FIGURE S1 – NUMBER OF AUTHORISED MEDICINAL PRODUCTS WITH A MANUFACTURING SITE PER COUNTRY - ACTIVE PHARMACEUTICAL INGREDIENT (API) AND FINISHED PHARMACEUTICAL PRODUCT (FPP)\*



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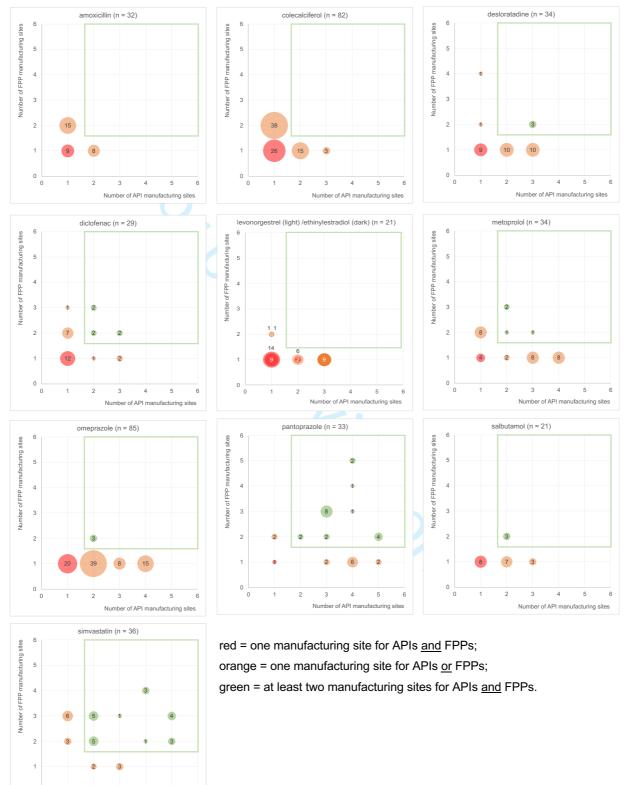
\* the sum of the products may be higher than the total number of products since a regulatory dossier for an authorised medicinal product may list manufacturers located in different countries

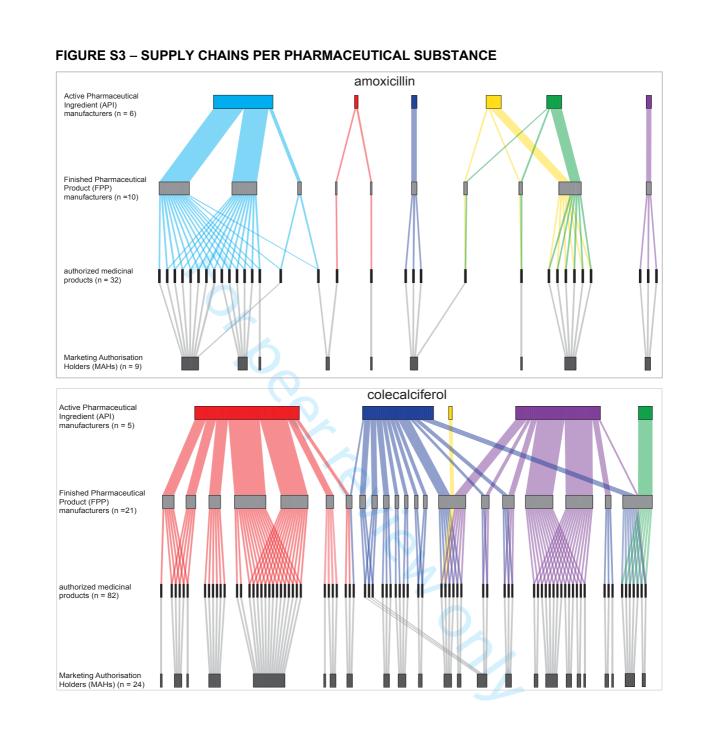
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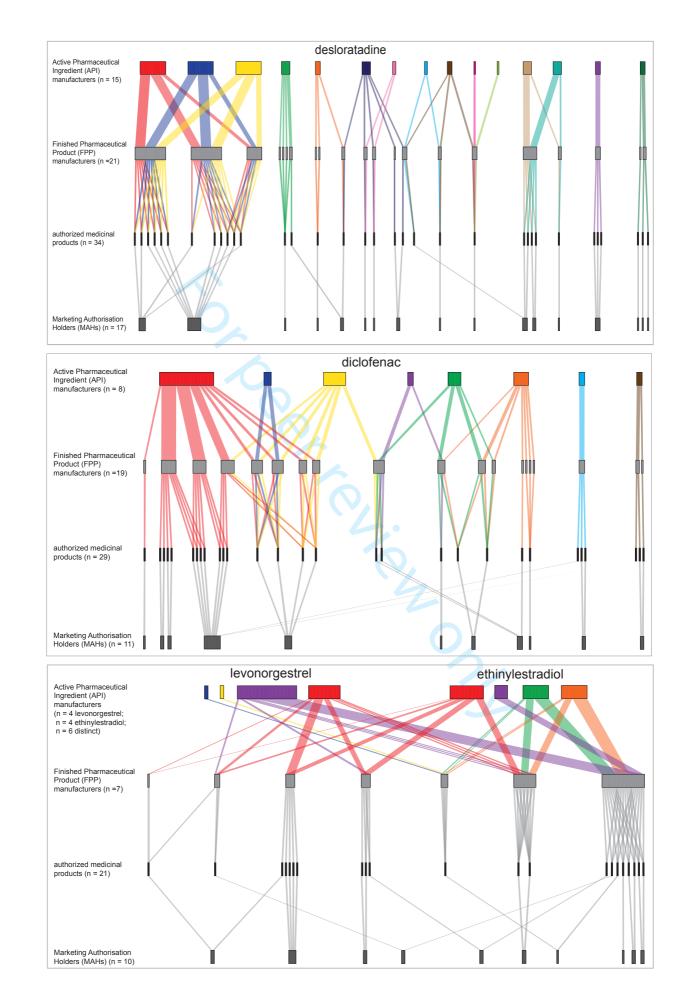
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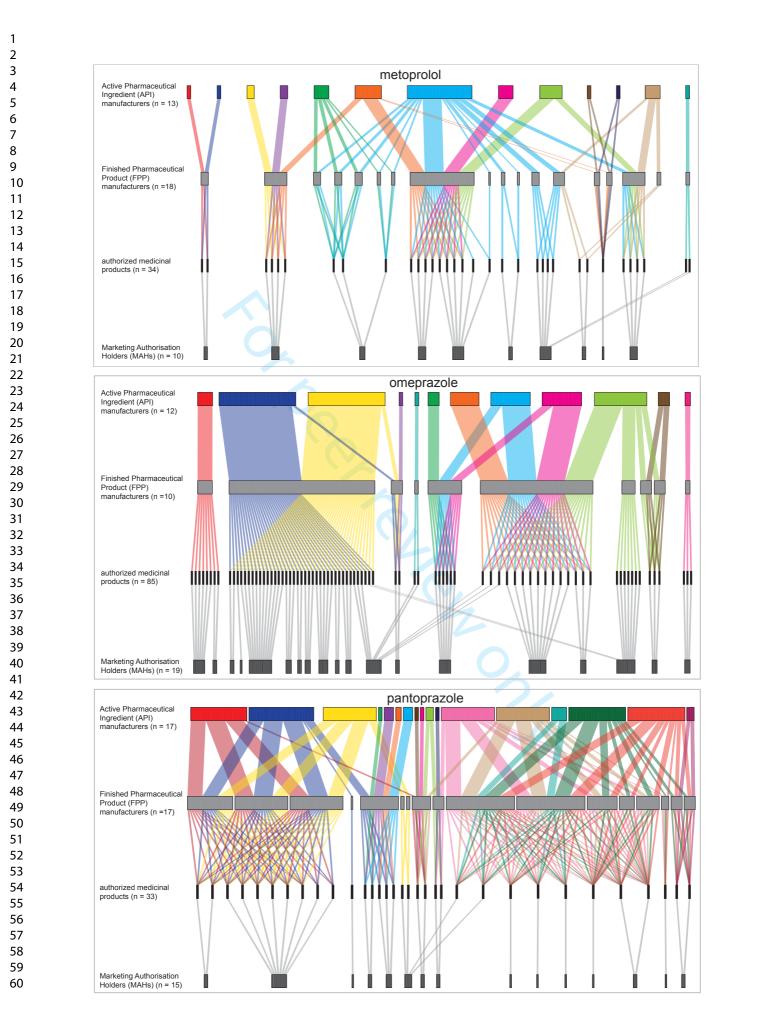
## FIGURE S2 – NUMBER OF MANUFACTURING SITES PER AUTHORISED MEDICINAL PRODUCT - ACTIVE PHARMACEUTICAL INGREDIENT (API) AND FINISHED PHARMACEUTICAL PRODUCT (FPP)



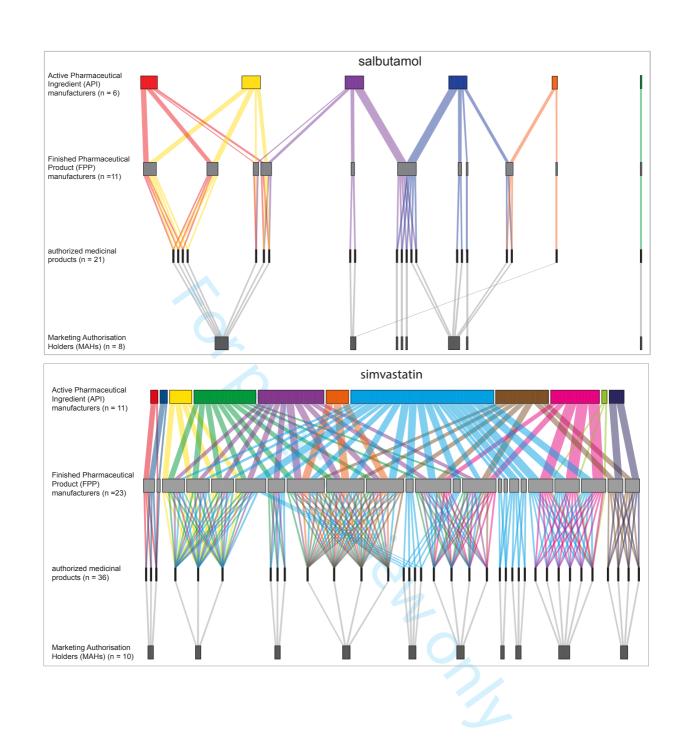




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(% of population)amoxicillinJ01CA04bacterial infection815,000 (4.7)colecalciferolA11CC05vitamin D deficiency1,005,000 (5.8)desloratadineR06AX27allergy740,000 (4.3)diclofenacM01AB05pain815,000 (4.7)levonorgestrel/ ethinylestradiolG03AA07contraception1,000,000 (5.7)metoprololC07AB02high blood pressure1,010,000 (5.8)	-	total         32           82         34	oral 32 82	25. Downloaded from http://bmjopen.bmj.com/ nement Superieur (ABES) . 2010 2011 2011 2011 2011 2011 2011 2011	rectal	authorisation holders (MAHs
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#### TABLE S2 – AUTHORISED MEDICINAL PRODUCTS RELYING ON ONE (AND THE SAME) API OR FPP MANUFACTURER

pharmaceutical	number of authorised medicinal products			
substance	total	one API manufacturer	one and the same API manufacturer	
amoxicillin	32	24 (75%)	16 (50%)	
colecalciferol	82	64 (78%)	34 (41%)	
desloratadine	34	11 (32%)	3 (9%)	
diclofenac	29	20 (69%)	12 (41%)	
levonorgestrel /	21	15 (71%)	7 (33%)	
ethinylestradiol	21	10 (48%)	10 (48%)	
metoprolol	34	12 (35%)	8 (24%)	
omeprazole	85	20 (24%)	8 (9%)	
pantoprazole	33	3 (9%)	2 (6%)	
salbutamol	21	8 (38%)	1 (5%)	
simvastatin	36	9 (25%)	9 (25%)	

#### A. Active pharmaceutical ingredient (API) manufacturer

#### B. Finished pharmaceutical product (FPP) manufacturer

pharmaceutical	number of authorised medicinal products				
substance	total	one FPP manufacturer	one and the same FPP manufacturer		
amoxicillin	32	17 (53%)	6 (19%)		
colecalciferol	82	44 (54%)	7 (9%)		
desloratadine	34	29 (85%)	6 (7%)		
diclofenac	29	15 (52%)	4 (14%)		
levonorgestrel /	21	20 (95%)	8 (38%)		
ethinylestradiol	21	20 (33 %)	0 (00 %)		
metoprolol	34	22 (65%)	9 (26%)		
omeprazole	85	82 (86%)	39 (46%)		
pantoprazole	33	11 (31%)	5 (14%)		
salbutamol	21	18 (86%)	5 (24%)		
simvastatin	36	5 (31%)	3 (8%)		