

## Supplementary Materials for

### **“Inactive” ingredients in oral medications**

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## **Materials and Methods**

### *Analysis of piece weights of medications*

We extracted a list of available dosages of the top 18 most prescribed active ingredients. (22) Oral solid dosage forms were selected according to availability through the Brigham and Women's Hospital (BWH, Boston, MA) pharmacy. The final dataset consisted of 54 unique medications (Table S1). Data regarding the active ingredient content in these medications was manually curated from Pillbox (<https://pillbox.nlm.nih.gov>), DailyMed (<https://dailymed.nlm.nih.gov/>), as well as directly *via* the web resources of the manufacturers. Dosage was converted for salt forms to ensure that actual mass of included active ingredient was considered in subsequent calculations. Medications were individually unpacked and immediately weighed to reduce impact of humidity absorption. Oral solids were individually weighed in triplicates on an APX-60 scale. The heaviest and lightest agents were re-measured on a Mettler Toledo scale to ensure reproducibility. A total of seven medications were included that shared the same active ingredient and dose compared to another medication in our list to investigate variability between producers and from production by the same manufacturer. Data analysis was performed in Microsoft Excel (Version 2013). To enhance the scope of this analysis, we also manually extracted data from the German provider "Gelbe Liste" ([www.gelbe-liste.de](http://www.gelbe-liste.de); accessed April 10, 2018) which lists piece weights of medications among their active ingredient mass. Manual curation of this data lead to a larger dataset of 1,902 medication weights and their active ingredient mass. This dataset was subsequently analyzed in Python (version 2.7.6) to extract percentage of mass of every medication corresponding to the mass of the inactive ingredients. Data was used with permission by "Gelbe Liste" (personal communication Ellen Reifferscheid).

### *Formulation Data*

The NIH Pillbox database (version 201605, <https://pillbox.nlm.nih.gov>) was downloaded in CSV format. Data was processed in KNIME (version 3.2) and Python (version 2.7.6). For data curation, we removed brackets, transformed ingredient names into lowercase, removed special characters (dots, commas, ampersands), unified numbering in names (e.g. "#", "No."), and removed duplicated, trailing, and leading spaces. Furthermore, commonly occurring misspellings or alternative spellings were corrected (see Table S5) and commonly occurring differences in word orders were standardized. Through this curation, we reduced the size of the database from

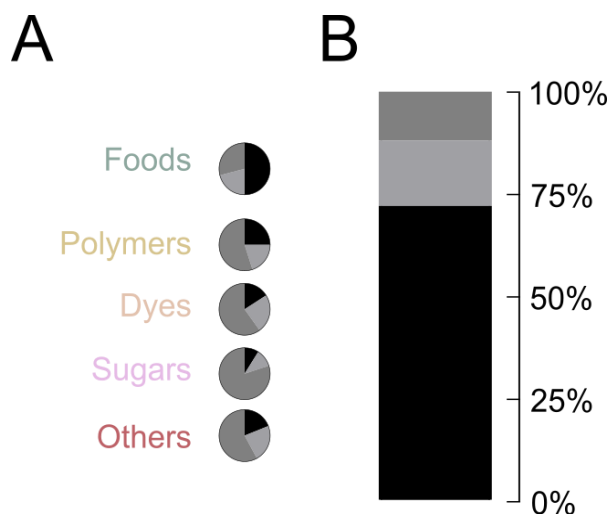
2,504 inactive ingredient entries to 1,154 unique entries (Figure S2). The inactive ingredient portion within a medication was defined as a unique combination of the different inactive ingredients, irrespective of their position in the ingredient list. Following this definition, a total number of 13,287 unique formulations were identified. Similar processing was applied to the active ingredients of medications, resulting in a total of 2,239 unique active ingredients, where an active ingredient is one or a combination of different active pharmaceutical ingredients (APIs). Data on the most commonly prescribed drugs was extracted from 2017 data from the IMS Institute. Data on commonly used GI medications were manually extracted for proton pump inhibitors, histamine 2 receptor blockers and treatments for irritable bowel syndrome (Figure 3).

#### *Identification of Inactive Ingredients as Allergens and Irritants*

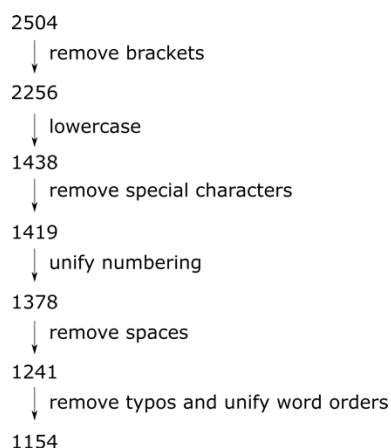
Raw counts of all PubMed entries for “excipient allergy” and “excipient irritation” were retrieved from the PubMed website (accessed on May 25, 2018) and exported into Prism for plotting. Reports of inactive ingredients were identified from Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>, accessed on August 16, 2017) by querying for reviews published in the past 25 years in English. The search terms looked for reviews with all permutations of the search terms “excipient” or “inactive ingredient” combined with either “allergy”, “adverse reaction”, or “reaction”. 128 unique articles were initially reviewed (Table S3). Abstracts and titles were reviewed to exclude studies that were focused on injectable or topical medications, were not discussing inactive ingredients, were written in a language other than English, or were otherwise out of scope for this study. 20 papers were ultimately included and lead to the identification of 38 inactive ingredients that have previously been reported to lead to classic allergic reactions in patients.

#### *Statistical analysis and plotting*

Data was analyzed in Python (version 2.7.6) using the Numpy ([www.numpy.org](http://www.numpy.org)) and SciPy ([www.scipy.org](http://www.scipy.org)) libraries. Networks were generated in Gephi (version 0.9.2; [www.gephi.org](http://www.gephi.org)) using the Yifan Hu layout algorithm with standard parameters. Survey data was visualized using SankeyMatic ([www.sankeymatic.com](http://www.sankeymatic.com)). Other plots were generated using matplotlib ([www.matplotlib.org](http://www.matplotlib.org)). All plots were processed in Inkscape (version 0.91). Statistical tests and statistical analysis was performed in Python (version 2.7.6).



**Fig. S1. Summary statistics for different allergen classes of potential allergens. (A)** Pie charts showcase the percentage of drugs where all formulations contain at least one allergen from the allergen ingredient classes (food, polymers, dyes, sugars, others), dark gray corresponds to drugs where all available medications are free of such potentially allergy-inducing inactive ingredients belonging to those classes, while light gray highlights drugs where some but not all formulations contain at least one ingredient from these classes. **(B)** Overall potential allergen content in different formulations of active ingredients. A total of 72% of APIs have all their medications contain at least one of these allergy-associated inactive ingredients (black bar). Only medications for 12% of APIs are completely free of concerning inactive ingredients (dark grey bar), while 16% of APIs have medications for which at least one allergen-free formulation exists (light grey bar).



**Fig. S2. Flowchart of data curation strategy for Pillbox extraction.** Numbers refer to the number of unique inactive ingredients names captured in the database after every curation step. Through this curation, we reduced the number of inactive ingredients in the Pillbox database to 1154 (46% of original database) by removing 1350 alternative spellings and misspellings.

**Table S1. Piece weight analysis of different versions of most commonly prescribed medications.**

Active ingredient	Dose	Producer	Weight1	Weight2	Weight3	% Inactive
amlodipine	2.5 mg	Major Pharma	49.3	49.0	48.9	92.93%
	5 mg	AvKARE/AvPAK	202.1	202.0	202.2	96.57%
	10 mg	McKesson	203.9	203.7	203.6	93.19%
amoxicillin	250 mg	NorthStar Rx	379.2	379.0	379.1	34.05%
	500 mg	NorthStar Rx	717.0	717.3	716.5	30.26%
Atorvastatin	20 mg	AvKARE/AvPAK	206.4	206.0	206.1	89.50%
	80 mg	Major Pharma	856.3	857.0	856.7	89.89%
azithromycin	250 mg	American Health Packaging	463.3	463.2	462.8	44.72%
	600 mg	Teva	1052.4	1052.3	1052.3	41.61%
furosemide	20 mg	West Ward	85.3	85.5	85.4	76.58%
	40 mg	West Ward	168.6	168.2	168.6	76.26%
	80 mg	West Ward	339.8	339.7	339.6	76.45%

gabapentin	100 mg	McKesson	177.2	176.8	177.2	43.52%
	300 mg	McKesson	462.3	462.4	462.3	35.11%
	400 mg	McKesson	610.1	610.3	609.8	34.43%
hydrochlorothiazide	25 mg	McKesson	110.5	110.7	110.5	77.39%
ibuprofen	200 mg	LNK	327.1	326.6	326.8	38.81%
	400 mg	McKesson	567.3	566.8	567.2	29.47%
	600 mg	McKesson	867.7	867.9	867.9	30.86%
	800 mg	McKesson	1179.8	1179.4	1179.6	32.18%
levothyroxine	25 mcg	Mylan Inst	130.2	129.7	130.0	99.98%
	50 mcg	Mylan Inst	129.0	128.8	128.9	99.96%
	75 mcg	Mylan Inst	130.1	129.6	130.0	99.94%
	88 mcg	Mylan Inst	131.2	130.8	131.0	99.93%
	100 mcg	Mylan Inst	128.6	128.7	128.4	99.92%
	112 mcg	Mylan Inst	130.6	130.5	130.2	99.91%
	125 mcg	Mylan Inst	129.8	129.5	129.6	99.90%
	125 mcg	AbbVie	128.9	130.2	129.6	99.90%
	125 mcg	AbbVie	131.1	131.2	130.7	99.90%
	137 mcg	Mylan Inst	128.8	128.8	129.2	99.89%
	150 mcg	Mylan Inst	130.1	130.0	129.9	99.88%
	200 mcg	AbbVie	132.3	131.9	131.7	99.85%
lisinopril	2.5 mg	Qualitest	97.0	96.9	96.6	97.42%
	5 mg	Major Pharma	106.9	106.8	106.7	95.32%
	10 mg	Major Pharma	213.6	213.9	213.6	95.32%
	20 mg	McKesson	194.9	194.6	194.7	89.73%
	20 mg	McKesson	195.8	195.9	196.4	89.80%
losartan	25 mg	McKesson	92.3	92.4	92.2	72.91%
	50 mg	McKesson	182.9	183.2	182.8	72.67%
metformin	500 mg	McKesson	602.6	602.1	602.5	17.00%
	850 mg	Major Pharma	961.6	961.6	961.8	11.61%
metoprolol tartrate	25 mg	American Health	146.9	146.7	146.3	83.75%

		Packaging				
	50 mg	American Health Packaging	291.7	292.0	291.7	83.67%
	50 mg	American Health Packaging	292.8	292.2	292.9	83.71%
	100 mg	American Health Packaging	482.6	484.4	482.3	80.27%
metoprolol succinate	25 mg	Major Pharma	102.3	102.3	102.0	75.54%
	50 mg	Major Pharma	205.5	205.1	205.9	75.67%
omeprazole	20 mg	Major Pharma	309.9	310.1	309.7	93.55%
sertraline	25 mg	American Health Packaging	78.2	78.1	77.6	64.16%
	50 mg	American Health Packaging	153.8	153.7	153.4	63.63%
	100 mg	American Health Packaging	307.6	307.7	307.8	63.68%
simvastatin	5 mg	McKesson	49.9	49.9	50.0	89.99%
	10 mg	McKesson	100.8	100.8	100.3	90.06%
	20 mg	McKesson	204.2	203.9	204.2	90.20%

**Table S2. Top 10 most common inactive ingredients in Pillbox.**

<b>Inactive ingredient</b>	<b>Number of occurrences in Pillbox (total 42,052)</b>
magnesium stearate	30,263 (72%)
microcrystalline cellulose	23,325 (55%)
titanium dioxide	21,125 (50%)
silicon dioxide	15,612 (37%)
starch corn	15,405 (37%)
lactose monohydrate	11,658 (28%)
hypromelloses	11,547 (27%)
talc	10,472 (25%)
croscarmellose sodium	8760 (21%)
polyethylene glycols	8282 (20%)



**Table S3. List of publications analyzed for identification of reports of allergic reactions or gastrointestinal side effects through inactive ingredients in medications.**

<b>PMID</b>	<b>Included?</b>	<b>Extracted inactive ingredients or reason to exclude</b>
28684647	Yes	Parabens and benzoates
28613520	No	Not relevant
28163222	No	Not relevant
27882527	No	Not relevant
27834127	Yes	Carboxymethylcellulose (CMC), povidones, PEG (macrogols), sulfites, benzyl alcohol, and tweens
27712572	Yes	Polyethylene glycol (PEG)
27534768	No	Inhaled medications
28827390	Yes	Wheat starch, peanut oil/arachis oil, benzyl alcohol
27491381	No	Not relevant
27436328	No	Not relevant
27196817	Yes	PEG, polysorbates (Tweens), poloxamers, PEG castor oils, laureth-9, cetomacrogol, PEG 40 stearate, cetomacrogol 1000, PEG 6000, polysorbate 80, hydroxyethylated starch, poloxamer, polysorbate 80
27128715	No	Environmental
26636421	No	Not relevant
26419538	No	Topical medications
26211812	Yes	Succinate esters, carboxymethylcellulose (CMC), polyethylene glycol (PEG; macrogol), lactose
26156542	No	Topical medications
25885102	No	Topical medications
25764151	No	Inhaled medications
25751935	No	Injections
25514481	No	Nasal and respiratory delivery only
25384223	No	Topical drugs
25341165	No	Injections
25017684	Yes	Carboxymethylcellulose (also called carmellose or croscarmellose,

		sodium carboxymethylcellulose, and E466), tartrazine, FD&C Blue No. 1 (bright blue), Blue No. 2 (indigo carmine), orange disperse 3 (Sunset Yellow), Povidone (PVP, polyvinylpyrrolidone), Sodium benzoate (E211), sulfites
25017683	No	Topical drugs
24878443	Yes	Gelatin, milk, casein, lactose, lactulose
24832168	No	Topical drugs
24714850	No	Injections
24674688	No	Injections
24656778	No	Topical drugs
24565702	No	Not relevant
24559657	No	Not relevant
24456019	No	Topical drugs
24173385	No	No adverse effects reported
24051350	No	Injections
24002150	No	Topical drugs
23765411	No	No inactive ingredients discussed
23730887	No	All IV or SC formulations
23544966	No	Inhaled medications
23543606	No	No adverse effects reported
23504430	No	Not relevant
23340678	No	Not relevant
23339763	No	Not relevant
23292495	No	Injections
25674402	No	Focus on delivery properties instead of adverse reactions
23243989	No	Japanese article
23238161	No	Injections
22833905	No	No focus on adverse events
22707362	No	Focus on stability instead of adverse events
22394125	No	Topical drug

22312932	Yes	Casein, lactose, banana essence, vanilla, vanillin
24300191	No	Ophthalmic products
22099411	No	French article
21801484	No	Not relevant
21787819	No	Nanomedicines
21741802	No	Treatment
21626047	No	Nutritional supplements
21611683	No	Topical
21199198	No	Inhaled medications
20949699	No	Subcutaneous injection
20861601	No	Parenteral
20517534	No	Parenteral
20185893	No	Topical drug
20128230	Yes	Carboxymethylcellulose (also called CMC, carmelose)
20013666	No	Otic drops
19732201	Yes	Indigo carmine (E132), sunset yellow, quinoline yellow
19580371	Yes	Corn syrup, benzalkonium chloride, allura red (E129; FD&C Red No 40), brilliant blue (E133; FD&C Blue No 1), erythrosine (E127; FD&C Red No 3), indigo carmine (E132; FD&C Blue No 2), Sunset yellow (E110; FD&C Yellow No 6), tartrazine (E102; FD&C Yellow No 5)
19567843	Yes	Methylhydroxybenzoate, propylhydroxybenzoate, cetyl alcohol, stearyl alcohol, polysorbate 80, arachis oil
19467048	No	Topical dental
19240542	No	Topical/ocular drugs
18845195	No	Topical/ocular drugs
18830864	No	Generally topical
18497245	No	German, topical
17159596	No	Parenteral
17037081	No	Preserving transplants

17017934	No	Ophthalmic products
16960822	No	Focused on chemical reactions
16868222	No	Comparing opioid formulations
16792601	No	Discussion of allergen tolerance
16572992	No	Chinese
16303277	No	Discussion of terms, not the products
16180936	No	Discussion of terms, not the products
16018907	No	Ingredient discussed is only used in parenterals; it isn't in pillbox
15996453	No	Parenteral
15788144	No	Topical sunscreens
15778049	No	Focused on chemical reactions
15714807	No	Chinese
14977910	No	Parenteral
13679965	No	Spanish
12964493	Yes	Amaranth, benzalkonium chloride, sunset yellow, parabens, peanut oil, ponceau, sulfites, tartrazine, brilliant black BN (E151), carmoisine (E122, azorubine), Bronopol, Castor Oil, Corn starch, mercury, Sesame Oil, Soybean oil
12871181	Yes	Carboxymethylcellulose
12721396	No	Parenteral, focus on actives
12614517	No	Topical, focus on microbicides
12042063	No	Topical/ocular drugs
11392448	No	Parenteral
11392447	No	Parenteral
11361009	No	Focused on chemical reactions
11325479	No	Focused on chemical reactions
11135703	No	Parenteral
10502611	No	Focused on pharmaceutical properties
10229638	No	Focused on breakdown of protein/peptide products
9057785	Yes	Diethylene glycol

9024461	Yes	Sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite, Aspartame, Saccharin, tartrazine (FD&C Yellow No. 5), sunset yellow, new cocchine, amaranth, erythrosine, indigo carmine (FD&C Blue No. 2), ponceau, Brilliant Blue (FD&C Blue No. 1), methyl blue, quinolone yellow, FD&C Red No. 40, lactose, propylene glycol, Benzalkonium chloride, Allura red (E129; FD&C Red No 40), Brilliant blue (E133; FD&C Blue No 1), Erythrosine (E127; FD&C Red No 3), Indigo carmine (E132; FD&C Blue No 2), Sunset yellow (E110; FD&C Yellow No 6), Tartrazine (E102; FD&C Yellow No 5)
8877241	Yes	FD&C yellow #5 ( tartrazine), FD&C yellow #6 (sunset yellow), FD&C Blue #1, FD&C Blue #2, carmine color, methylparaben, propylparaben, aspartame, mannitol, sucrose
8766194	No	Inhaled medications
8644576	No	Topical/ocular drugs
8729891	No	Parenteral
8571282	No	French
7600718	No	Topical sunscreens
8535931	Yes	Carboxymethylcellulose, sulfur dioxide, Tartrazine (yellow dye No. 5, E 102), ponceau, erythrosine, Benzoic acid, Aminobenzoic acid, para-hydroxybenzoic acid (parabens)
7551218	No	Used for injected medications
7842686	No	Topical meds
8378865	No	German
7912532	No	Injections
1421646	No	Reaction to katerolac, an active ingredient
1497796	No	Parenteral/sc

**Table S4. Lactose content of various medications.**

<b>Drug</b>	<b>Lactose content [mg]</b>	<b>Pubmed ID</b>
Allegron 10 mg (Nortriptyline)	38.00	19035974
Allopurinol	57.00-171.00	24732384
Amitryptiline 10 mg	43.00	19035974
Amlodipine	140.00-151.00	24732384
Asacol MR 400 mg (Mesalazine)	75.0	19035974
Azathioprine	34.36-116.00	24732384
Bisoprolol	1.26-136.00	24732384
Budenofalk 3 mg (Budesonide)	600.0	19035974
Capecitabine	7.00-68.95	24732384
Celevac 500 mg (Methylcelluose)	27.70	19035974
Citalopram 20 mg	45.00	19035974
Clozapine	32.44-281.62	24732384
Codeine phosphate 30 mg	46.00	19035974
Colofac 135 mg (Mebeverine HCl)	95.00	19035974
Delta-cortil 5 mg (Prednisolone)	31.0	19035974
Destolit 150 mg (Ursodeoxycholic acid)	78.00	19035974
Domperidone 10 mg	56.00	19035974
Dulco-Lax 5 mg (Bisacodyl)	41.00	19035974
Enalapril	78.00-253.60	24732384
Fluconazole	16.60-210.00	24732384
Imodium 2 mg (Loperamide HCl)	108.00	19035974
Imodium 2 mg (Loperamide HCl)	125.00	19035974
Imuran 50 mg (Azathioprine)	71.0	19035974
Levofloxacin	3.60-26.45	24732384
Loratadine	62.50-75.00	24732384
Losartan	4.50-231.60	24732384

Losec 40 mg (Omeprazole)	4.00	19035974
Mebeverine hydrochloride 135 mg	99.00	19035974
Merbentyl 10 mg (Dicycloverine HCl)	74.00	19035974
Mesren MR 400 mg (Mesalazine)	77.0	19035974
Methotrexate 2.5 mg (Methotrexate)	28.9	19035974
Metoclopramide 10 mg	71.00	19035974
Morphine 10 mg	90.00	21766071
Morphine 30 mg	70.00	21766071
Nevirapine	168.00-464.00	24732384
OxyContin 10 mg (Oxycodone)	69.25	21766071
OxyContin 20 mg (Oxycodone)	59.25	21766071
OxyContin 40 mg (Oxycodone)	32.25	21766071
OxyContin 80 mg (Oxycodone)	78.50	21766071
Pancrex V tablets (Pancreatin)	54.00	19035974
Prednisolone 2.5 mg	56.0	19035974
Pro-banthine 15 mg (Propantheline Br)	38.00	19035974
Prochlorperazine 5 mg	70.00	19035974
Puri-Nethol 50 mg (Mercaptopurine)	61.0	19035974
Senokot 7.5 mg (Senna)	16.00	19035974
Simvastatin	35.00-576.24	24732384
Zoton Fastab 30 mg (Lansoprazole)	28.00	19035974

**Table S5. Corrected and identified misspellings or alternative spellings in the Pillbox database.**

<u>Ingredient name</u>	<u>Identified misspellings or alternative spellings</u>
sulfate	sulphate
glycolate	glycollate
stearyl	steryl
dioxide	dioxde
triacetin	tracetin
tricalcium phosphate	tribasic calcium phosphate
dihydrate	dehydrate
gallate	gallette
pregelatinized	pregenatinized, pregelatinzed, pregelatinised, pregalatinized, pregelitanized
povidone	povidine
polyethylene	polyehtylene
polydextrose	polydestrose
polacrilin	polacrillin
grandiflorus	grandiflorum
oleic	olealic
microcrystalline	mircocrystalline, microcrystalline, microcrystaline, micro-crystalline
parabens	paraben
copolymer	co-polymer
stearate	sterate, strearate, searate
macrogol	macrogel
oxide	oxides
methylcellulose	methylcellulose, methyl cellulose, methycellulose
monohydrate	mohydrate, mohydrte, monhydrate
hydroxypropyl	hydroxypropl, hydroxipropyl, hydroxy propyl
vegetable	vegtable



ethylcelluloses	ethylcellulose, ethyl-cellulose
croscarmellose	croscramellose
crospovidone	crospovidine, crospovidone
corn starch	cornstarch
colloidal	collidiol, collloidal, collodial, colloidal, collidiol, colloidol
silicon	silicone, solicon, sillicon
carboxymethylcellulose	carboxymethyl cellulose
aluminium	aluminum, alumina
alpha-lipoic	alpha lipoic
anhydrous	anhdrous, anyhydrous
acetaminophen	acetamiphen
monooleate	mooleate
croscarmellose	crosscarmellose