Review of purchases of unapproved medications by the Veterans Health Administration

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Ron L. Carico Jr., Pharm.D., M.P.H., Marshall Health, Huntington, WV.

Thomas R. Emmendorfer, Pharm.D., VA Pharmacy Benefits Management Services, Washington, DC.

Sherrie L. Aspinall, Pharm.D., M.Sc., VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, and VA Center for Medication Safety, Pharmacy Benefits Management Services, Hines, IL.

Margaret T. Mizah, Pharm.D., St. Clair Hospital, Pittsburgh, PA.

Chester B. Good, M.D., M.P.H., VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, and VA Center for Medication Safety, Pharmacy Benefits Management Services, Hines, IL.

Address correspondence to Dr. Aspinall (sherrie.aspinall@va.gov).

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Purpose. Many medications that were marketed prior to 1962 but lack Food and Drug Administration (FDA) approval are prescribed in the United States. Usage patterns of these "unapproved medications" are poorly elucidated, which is concerning due to potential lack of data on safety and efficacy. The purpose of this project was to characterize purchases of unapproved medications within the Veterans Health Administration (VHA) by type, frequency, and cost.

Methods. VHA purchasing databases were used to create a list of all products with National Drug Codes (NDCs) purchased nationwide in fiscal year 2016 (FY16). This list was compared to FDA databases to identify unapproved prescription medications. For each identified combination of active pharmaceutical ingredient (API) and route of administration ("API/route combination"), numbers of packages purchased and associated costs were added.

Results. VHA pharmacy purchasing records contained 3,299 unapproved products with NDCs in FY16. After excluding equipment, nutrition products, compounding ingredients, nonmedication products, and duplicate NDCs, there were 600 unique NDCs associated with 130 distinct API/route combinations. The most commonly acquired product was prescription sodium fluoride dental paste (350,775 packages). The greatest pharmaceutical expenditure was for sodium hyaluronate injection ($24.5 million). Unapproved products accounted for less than 1% of overall VHA pharmacy purchasing in FY16.

Conclusion. VHA purchased many unapproved prescription products in FY16 but is taking action to address use of such products in consideration of safety and efficacy data and available alternatives.

Keywords: drug approval; pharmacy administration; pharmacy and therapeutics committee; quality assurance, healthcare; U.S. Food and Drug Administration

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The Food and Drug Administration (FDA) has estimated that approximately 2% of all drug products marketed in the United States are "unapproved," a legal categorization given to medications that have not been approved as both safe and efficacious[1]; essentially, an unapproved prescription medication only has off-label indications. Unapproved medications were initially permitted on the market due to the history of U.S. pharmacy legislation, but FDA has taken steps in recent years to bring all unapproved drugs into compliance with modern legal requirements,[2] with recent efforts targeting such diverse items as cough and cold products,[3-9] quinine,[10] and even veterinary thyroid products.[11] As unapproved drugs may or may not have undergone systematic and rigorous safety and efficacy testing, the use of unapproved drugs is a potential patient safety issue. For example, FDA acted to remove unapproved ergotamine-containing oral products from the market,[12] in part due to rare but serious cardiovascular risks.[13] Approved ergotamine is labeled for limited use

with a related boxed warning; unapproved products did not always carry the warning.[12] Trimethobenzamide suppositories were removed from the market in 2007 due to a lack of efficacy data for their most common clinical indication, nausea.[14]

Oftentimes, unapproved medications can be marketed because they were available prior to the establishment of FDA. The Food, Drug, and Cosmetic Act (FDCA) of 1938 created the precursor to FDA, defined "drug" in legal contexts, and required that all new drugs be tested for safety.[15–17] Drugs marketed before 1938 were not impacted by this ruling provided that their composition and labeling did not change.[2,15] The requirement that efficacy also be demonstrated by new drugs was established by the 1962 Kefauver-Harris Amendment to the FDCA, which also attempted to bring drugs approved between 1938 and 1962 into compliance with newer laws.[3,15] At no point were previously marketed drugs systematically removed from the market due to failure to meet the legal requirements of the FDCA or the Kefauver-Harris Amendment.

Thus, drugs brought to market before 1938 or deemed "identical, related, or similar" (IRS) to such drugs have never been proven safe to FDA; indeed, it is the opinion of FDA that most drugs marketed prior to 1938 are sold illegally, as they have likely undergone significant variation over time and can therefore no longer be claimed to have IRS status.[2] Meanwhile, drugs brought to market between 1938 and 1962 have been part of an ongoing systematic review of efficacy—the Drug Efficacy Study Implementation (DESI) program.[3] Any drug brought to market before 1938 that is claimed to be IRS to any drug brought to market before 1938 or is being reviewed by the DESI program is technically unapproved by FDA.

Complete lists of unapproved medications are not routinely published, which makes the prevalence of unapproved medication use difficult to assess across healthcare systems. FDA has criteria to prioritize unapproved medication reviews: drugs that present potential safety risks are given highest priority, followed by drugs that lack evidence of efficacy, drugs that are promoted fraudulently, drugs that present direct challenges to the current approval process (e.g., by directly competing with approved drugs), drugs that violate the FDCA in other ways, and, finally, drugs whose formulations have been changed primarily to avoid enforcement action.[2] An unapproved medication may fit into more than one of these categories.

To our knowledge, only 1 assessment of unapproved medication use in a healthcare system has been published; that administrative case study outlined the decision-making process used by a single hospital to revisit the formulary status of pre-1938 medications. At the conclusion of that process, the number of nonformulary, pre-1938 products increased by 10 (from 41 to 51 of 88 products reviewed).[18] Vertically integrated healthcare systems, such as the Veterans Health Administration (VHA), are in a unique position to review usage patterns of unapproved drugs across both outpatient and inpatient services. The primary purpose of the quality improvement project described here was to evaluate the types, frequencies, and costs of unapproved medication purchasing in VHA to help prioritize discussions of unapproved medications with potential safety and efficacy concerns.

KEY POINTS

- Unapproved prescription medications that have not been formally assessed for efficacy and safety by the Food and Drug Administration (FDA) remain on the market.
- The Veterans Health Administration (VHA) reviewed its purchases of unapproved prescription medications, stratifying purchased products by route of administration; examination of individual unapproved medications is an ongoing quality improvement project.
- Other healthcare organizations and FDA should continue to review unapproved medication use; VHA's methodology and list of unapproved medications may be helpful in such reviews.

Methods

A list of all products with National Drug Codes (NDCs) purchased by VHA in fiscal year 2016 (FY16), along with associated costs, was cross-referenced with FDA's electronic Drug Registration and Listing System (eDRLS), a database of products known by FDA to be marketed in the United States. The VHA data captured pharmacy purchases intended for both inpatient and outpatient use. Products that were not listed in eDRLS (categorized for our project as "unlisted unapproved") or that were listed by eDRLS with a legal status of "unapproved" (categorized as "listed unapproved") were retained for analysis. The result was a preliminary table of unapproved products with NDCs purchased by VHA in FY16, with the number of packages obtained listed for each NDC. To verify the approval status and identity of unlisted products, each NDC was also checked against FDA's Orange Book and National Drug Code Directory websites[19,20] or the National Institutes of Health's DailyMed website.[21] If an NDC could not be otherwise identified, an Internet search was performed to attempt to locate manufacturer labeling.

Once products with NDCs had been definitively identified, a series of exclusions were applied to limit the analysis to products that were classified as drugs; as medical devices; or as "medical foods," defined as products that (1) are absorbed systemically or applied to the eyes and (2) exert a therapeutic effect due to the presence of a chemical compound that is not produced

endogenously or normally ingested as a typical component of food. We excluded nonmedication products such as syringes for insulin injection and bandages for wound care, nutritional supplements (e.g., food thickeners), and compounding ingredients (e.g., 70% sorbitol) while including "drug-like" agents that alter bodily function in ways not tied to nutrition, such as the medical food caprylic triglyceride (marketed for dietary management of patients with Alzheimer's disease) and the medical device intraarticular hyaluronic acid (marketed under various trade names for treatment of knee pain in patients with osteoarthritis). We also excluded unapproved products available without a prescription, as the premarketing approval process for these products carries a different burden of regulatory review.

The unapproved products list was categorized by active pharmaceutical ingredients (APIs) and then by route of administration, giving each item an operational definition such as "phenobarbital oral solid" or "tetracaine ophthalmic." Different dosage strengths of the same API and route of administration were grouped together as a single API. This categorization method was used to conform to FDA reports on quantities of drug products sold in the United States. Unapproved prescription multivitamins were grouped together for this analysis irrespective of type (e.g., prenatal). Prescription supplements (either medical foods or unapproved prescriptions) and topical wound care creams, gels, and ointments (either medical devices or unapproved prescriptions drugs) were similarly grouped. Then, the number of packages procured and the cost to VHA for each combination of API and route of administration ("API/route combination") were summed across all applicable NDCs, categorized by route of administration (i.e., oral, injectable, or other), and ranked by both number of packages obtained and cost.

For each API/route category, the Orange Book[19] and FDA online "NDC Lookup" tool[20] were consulted to see if another NDC in the same API/route category was approved for U.S. marketing. Labeled and off-label indications for each API/route category were checked using the website Clinical Pharmacology and Wolters Kluwer's Lexi-Comp service.[22,23] For each API/route category, the presence of an approved NDC within the category or the presence of another medication approved for the product's common uses was noted.

The project was reviewed and approved by the designated VHA program office in accordance with VHA policies describing operations activities that do and do not constitute research.[24] The program office determined that the evaluation was a nonresearch, quality improvement activity exempt from VHA human subjects research requirements.

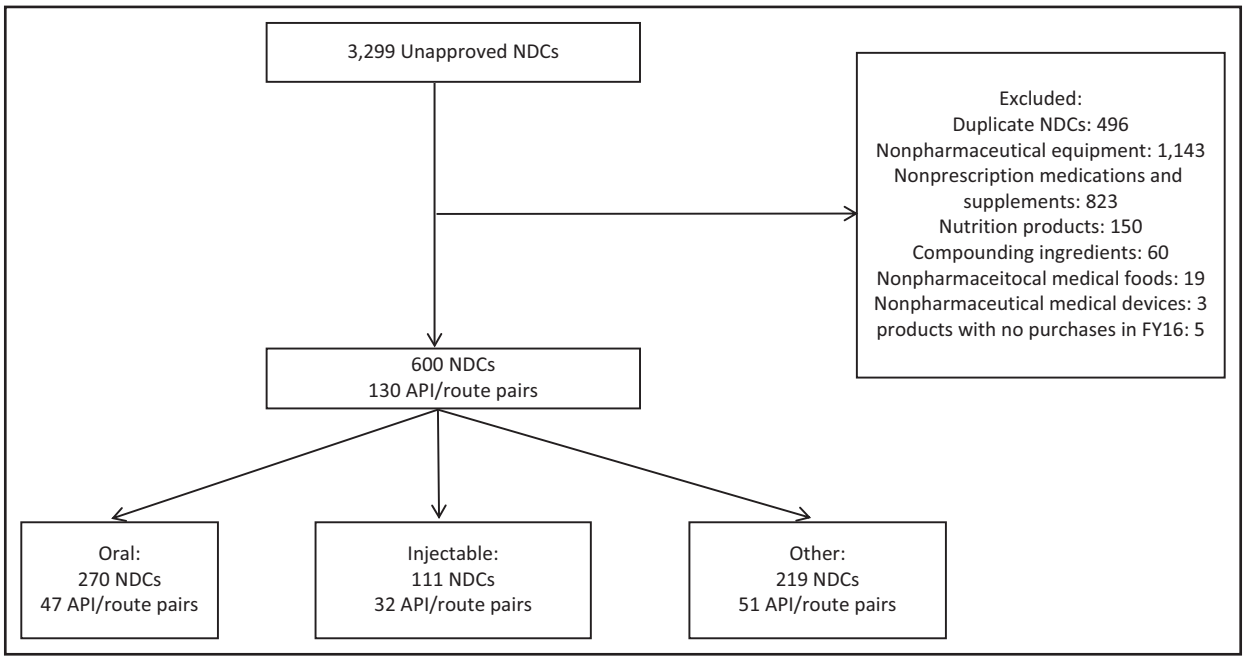
Results

VHA pharmacies obtained 3,299 products with unapproved NDCs in FY16; 496 of these represented duplicate entries arising from alternative spellings of product names and were excluded. The majority of the remaining exclusions (1,143 NDCs) were equipment (e.g., ostomy supplies, glucometers) or products available without a prescription (823 NDCs). Additionally, 150 NDCs were for nutritional products (e.g., food-thickening powders), 60 were for compounding ingredients (e.g., sorbitol), and 19 were for medical foods whose active ingredients were modified essential nutrients, such as methylated folate. Only 3 medical devices were excluded; all other medical devices were injectable, topical, or ophthalmic products with drug-like chemical or biochemical agents. A manual review found 5 NDC products of which no packages were purchased; these NDCs were also excluded. After the exclusions were applied, 600 unique NDC products involving 130 distinct API/route combinations remained for analysis (Figure 1). The full list of API/route combinations, with the number of associated NDCs for each, can be found in the supplementary materials (eAppendix).

Table 1 ranks the top 25 products by number of packages in each route of administration category. The product with the highest overall package count was prescription-strength sodium fluoride dental paste (350,775 packages), followed by ammonium lactate topical lotions and creams (143,053 packages). These were also the most commonly purchased nonoral, noninjectable products. The most commonly purchased injectable was the drug-like medical device hyaluronate intraarticular (109,101 packages); it also was the most frequently acquired product not listed in the Veterans Affairs (VA) national formulary. Other commonly purchased injectable products included 0.9% sodium chloride flush syringes (19,551 packages), ephedrine (14,127 packages), and sodium bicarbonate (8,426 packages). The most frequently acquired oral products were citric acid–sodium citrate liquid (17,392 packages), prescription multivitamin tablets (16,426 packages), salsalate tablets (10,191 packages), and hyoscyamine oral solids (9,170 packages).

The top 25 products by cost in each route of administration category are listed in Table 2. Sodium hyaluronate injection made up almost half of the costs of all analyzed products, with VHA spending in excess of $24 million on that product in FY16. Unapproved 0.9% sodium chloride flush syringes were the next highest-ranked injectable by cost (approximately $1.7 million), followed by unapproved sodium bicarbonate (approximately $1.3 million). Salsalate was the top-ranked unapproved oral product by cost (more than $3 million), followed by potassium chloride powder packets ($694,110) and opium tincture liquid ($449,042). The top-ranked nonoral, noninjectable product was hydrocortisone rectal ($2.4 million), followed by sodium fluoride dental paste (approximately $1.7 million) and benoxinate–fluorescein ophthalmic ($1.2 million). In general, unapproved injectables were the highest-ranked category by cost (almost $32 million in total), while

Figure 1. Flowchart of product selection for analysis. API = active pharmaceutical ingredient, NDC = National Drug Code, FY16 = fiscal year 2016.



unapproved oral medications were the lowest-ranked category (approximately $7.4 million in total).

Table 3 lists the top 25 products overall by number of packages purchased among NDC products without an FDA-approved alternative containing the same active ingredient and strength and delivered by the same route of administration. Potential approved prescription or nonprescription alternatives for the common uses of these unapproved products are also included in the table. The most frequently obtained items of this type were prescription sodium fluoride dental paste, followed by hydrocortisone rectal and benoxinate–fluorescein ophthalmic drops. In several cases (i.e., sodium fluoride dental, aluminum chloride hexahydrate topical, hydroquinone topical, urea topical, and phenazopyridine oral), products with the same active ingredients but different strengths are found in nonprescription formulations and may serve as potential options.

Discussion

To our knowledge, this is the first report regarding purchases of FDA-unapproved medications for inpatient and outpatient use by a large, integrated healthcare system, although a previously published case study addressed formulary decision-making processes pertaining to unapproved products that had been purchased once or more in the prior year at a single hospital.[18] In addition, we are not aware of any other published analysis that has attempted to list all unapproved medications in common use (eAppendix); this list should be of interest to stakeholders in healthcare, FDA, and industry. However, our primary interest was assessing the scope of unapproved medication use in order to prioritize ongoing internal discussions of safety and efficacy. We also found unapproved medications of which there were sizable purchases by VHA. Although expenditures for unapproved products totaled $51.6M in FY16, such unapproved products accounted for less than 1% of all pharmaceutical spending by VHA that fiscal year, which totaled $6.28 billion.[25] As that expenditure was less than 2% of all VHA spending on U.S. drug products FDA believes to be unapproved,[2] it appears that VHA may already be phasing out unapproved medication use in normal clinical processes and that the cost to VHA is negligible. Lastly, while most of the unapproved drugs have a long record of use, the continued use of these agents should prompt reviews for safety and efficacy and to determine whether other approved drugs might be more appropriate.

FDA has been reviewing unapproved drugs since the DESI program was launched in the early 1960s[2]; however, as our review indicates, many unapproved drugs remain on the market. Unless more resources and enforcement power are made available to FDA, regulatory review and action targeting all unapproved agents currently on the U.S. market may take decades.[2] Therefore, large healthcare organizations may wish to periodically review their use of unapproved medications, looking for products with potential safety and efficacy concerns. Many of the most frequently acquired unapproved items within the VHA system have already been internally reviewed. For instance, salsalate tablets have been found to have reasonable efficacy

Table 1. Top 25 Unapproved Products Identified Within VHA System, by Route of Administration and Number of Packages Purchased[a]

Oral		Injectable		Other (Topical, Rectal, Ophthalmic)	
Product	**Packages**	**Product**	**Packages**	**Product**	**Packages**
Citric acid–sodium citrate liquid[b]	17,483	Hyaluronate (device)	109,101	Sodium fluoride dental[b]	350,775
Multivitamin tablets	16,426	Saline flush[b] (device)	19,551	Ammonium lactate topical[b]	143,053
Salsalate tablets[b]	10,191	Ephedrine[b]	14,127	Hydrocortisone rectal[b]	84,440
Hyoscyamine tablets, capsules	9,170	Sodium bicarbonate[b]	8,426	Benoxinate–fluorescein ophthalmic[b]	32,240
Potassium phosphate–sodium biphosphate–sodium phosphate solid[b]	4,753	Epinephrine[b]	7,508	Tetracaine ophthalmic[b]	24,001
Phenobarbital solid[b]	4,647	Sodium chloride[b]	6,729	Aluminum chloride hexahydrate topical	10,211
Nitroglycerin sustained release solid	4,524	Atropine[b]	6,104	Sodium chloride inhalation (device)	9,812
Phenazopyridine solid[b]	4,130	Magnesium sulfate[b]	4,193	Wound care topical creams, gels, ointments	9,301
Potassium chloride solid[b]	3,124	Heparin flush[b] (device)	4,068	Ethyl chloride topical[b] (device)	7,726
Potassium chloride liquid[b]	2,949	Calcium chloride[b]	3,003	Urea topical[b]	7,572
Potassium bicarbonate solid[b]	2,739	Morphine[b]	2,894	Chondroitin ophthalmic[b] (device)	7,317
Thyroid solid	2,417	Calcium gluconate[b]	2,875	Hydroquinone topical[b]	6,918
Barium sulfate liquid	1,939	Hydromorphone[b]	1,701	Hyaluronate ophthalmic[b] (device)	4,672
Citric acid–potassium citrate–sodium citrate liquid[b]	1,275	Dextrose	1,485	Hypromellose ophthalmic[b]	4,635
Opium liquid	1,006	Methylene blue[b]	1,342	Hydrocortisone–pramoxine topical	4,616
Prescription supplements	858	Potassium phosphate[b]	1,332	Sulfacetamide–sulfur topical	3,242
Meclizine solid[b]	765	Vitamin c[b]	1,308	Fluorescein ophthalmic[b]	3,076
Citric acid–potassium citrate liquid[b]	740	Trace elements[b]	783	Silver nitrate topical[b]	2,852
Methenamine solid[b]	659	Papaverine	545	Belladonna–opium rectal[b]	2,753
Potassium iodide liquid[b]	407	Ethanol[b]	316	Chondroitin–hyaluronate ophthalmic (device)	2,166
Hyoscyamine liquid	375	Sodium phosphate[b]	201	Hydrocortisone–iodoquinol topical	1,962
Potassium phosphate solid	350	Tetracaine[b]	159	Salicylic acid topical[b]	1,751
Iodine–potassium iodide liquid	293	Phenobarbital[b]	158	Cocaine topical[b]	1,499
Acetaminophen–dichloralphenazone–isometheptene solid[b]	214	Physostigmine[b]	111	Lactic acid topical	1,266
Phenobarbital liquid[b]	204	Zinc sulfate[b]	81	Atropine ophthalmic	621
Others (22 items)	985	Others (7 items)	170	Others (26 items)	2,627
Total	92,623	Total	198,271	Total	731,104

[a]VHA = Veterans Health Administration.
[b]Veterans Affairs national formulary item.

Table 2. Top 25 Unapproved Products Identified Within VHA System, by Route of Administration and Cost[a]

Oral		Injectable		Other (Topical, Rectal, Ophthalmic)	
Product	**Cost ($)**	**Product**	**Cost ($)**	**Product**	**Cost ($)**
Salsalate tablets	3,509,134	Hyaluronate intraarticular	24,483,455	Hydrocortisone rectal	2,435,719
Potassium chloride powder packets	694,110	0.9% sodium chloride flush (device)	1,655,532	Sodium fluoride dental	1,696,898
Opium liquid	449,042	Sodium bicarbonate	1,320,494	Benoxinate–fluorescein ophthalmic	1,206,853
Phenazopyridine tablets	444,613	Methylene blue	776,106	Chondroitin ophthalmic (device)	1,076,410
Multivitamin tablets, capsules	347,669	Potassium phosphate	584,053	Belladonna–opium rectal	923,376
Barium sulfate oral suspension, cream	309,396	Calcium gluconate	506,047	Sulfacetamide–sulfur topical	720,990
Phenobarbital tablets	251,168	Epinephrine	337,502	Hyaluronate ophthalmic (device)	647,965
Hyoscyamine tablets	191,328	Ethanol	294,349	Hydrocortisone–pramoxine topical	456,604
Potassium phosphate–sodium biphosphate–sodium phosphate tablets	166,867	Atropine	254,096	Chondroitin–hyaluronate ophthalmic (device)	427,526
Nitroglycerin sustained-release solid	139,961	Calcium chloride	237,198	Ammonium lactate topical	406,167
Thyroid tablets	136,530	Ephedrine	230,501	Urea topical	378,768
Acetaminophen–dichloralphenazone–isometheptene capsules	67,784	Heparin flush (device)	202,820	Tetracaine ophthalmic	373,922
Citric acid–sodium citrate liquid	67,132	Trace elements	176,812	Hydroquinone topical	316,909
Potassium chloride liquid	63,577	Sodium chloride	166,604	Cocaine topical	266,712
Hyoscyamine–methenamine–methylene blue–phenyl salicylate–sodium phosphate tablets, capsules	56,280	Phenobarbital	125,026	Ethyl chloride topical (device)	221,783
Belladonna–phenobarbital liquid	54,844	Dextrose	113,246	Sodium chloride inhalation (device)	124,749
Prescription supplements	50,611	Vitamin c	101,127	Wound care topical gels, creams	119,757
Methenamine tablets	49,507	Sodium phosphate	81,274	Silver nitrate topical	108,386
Citric acid–potassium citrate liquid	36,065	Magnesium sulfate	56,199	Salicylic acid topical	73,599
Esterified estrogen–methyltestosterone tablets	33,881	Hydromorphone	34,766	Aluminum chloride hexahydrate topical	69,663
Acetaminophen–caffeine–isometheptene tablets	33,502	Morphine	23,155	Mineral oil, sterile topical	60,321
Potassium para-aminobenzoate capsules	28,200	Tetracaine	21,396	Mucosal protectants, buccal (device)	42,133

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Table 2. Top 25 Unapproved Products Identified Within VHA system, by Route of Administration and Cost[a]

Oral		Injectable		Other (Topical, Rectal, Ophthalmic)	
Product	**Cost ($)**	**Product**	**Cost ($)**	**Product**	**Cost ($)**
Hyoscyamine–methenamine–methylene blue–phenyl salicylate–benzoic acid tablets	26,679	Papaverine	20,924	Hydrocortisone–iodoquinol topical	38,731
Potassium bicarbonate tablets	25,633	Zinc sulfate	19,191	Saliva, artificial (device)	32,798
Belladonna–phenobarbital tablets	15,738	Amobarbital	8,797	Hypromellose ophthalmic	28,509
Others (22 items)	103,923	Others (7 items)	18,864	Others (26 items)	170,002
Total	7,353,173	Total	31,849,535	Total	12,425,251

[a]VHA = Veterans Health Administration.

and to pose lower risks of gastrointestinal bleeding than other nonsteroidal antiinflammatory drugs (NSAIDs)[26]; given VHA's large elderly patient population, that likely helps explain the purchase of approximately 6.2 million salsalate tablets by VHA at an average cost of $0.56 per tablet.

However, other widely used items may carry underappreciated risks or offer limited efficacy. Hyoscyamine is one of the top oral medications purchased, but it has strong anticholinergic adverse effects, with an incumbent increased risk of sedation and falls that makes it potentially unsafe in older patients.[27] Similar concerns are present with meclizine,[27] which has limited efficacy for its primary indication (treatment of chronic vertigo).[28] While opium oral liquid has been used to treat diarrhea,[29] particularly in short bowel syndrome,[30] other modalities are regarded as safer and more efficacious (e.g., loperamide or diphenoxylate).[31] Phenobarbital retains its place in guidelines for treatment of status epilepticus,[32] but studies suggest that it may be more sedating than other, newer antiepileptic drugs for chronic therapy.[33-35] Finally, oral desiccated thyroid is still used despite a lack of data and potentially significant variation among products produced by different manufacturers; the American Society of Clinical Endocrinologists recommends the use of levothyroxine instead.[36]

Unapproved medications with FDA-approved equivalents should be closely examined. Our review found extensive purchases of unapproved ephedrine injection despite the presence of approved NDC products starting in April 2016; however, shortages of ephedrine were reported in the first quarter of FY16.[37] Unapproved NDC products containing 4 different strengths of morphine injection were also purchased. Given the safety concerns with this drug and the availability of FDA-approved alternatives, it is surprising that unapproved morphine exists. In addition, we found widespread use of unapproved ammonium lactate lotion; interestingly, the manufacturer markets the lotion under both unapproved and approved NDCs. The reasons for use of the unapproved product within the VHA system were unclear. Additionally, regular reviews may identify medications that have gained FDA approval since the last review. For instance, tetracaine ophthalmic solution was approved by FDA in 2016,[38] and cocaine intranasal was approved in 2017.[39] Barring product shortages, these approvals should lead to detection of a decrease in VHA's purchase of the corresponding unapproved products during subsequent reviews.

For unapproved products without safety and/or efficacy concerns and without FDA-approved equivalents, continued use should be placed in the context of alternate approved products and the available literature, as VHA has done with salsalate and other NSAIDs. However, those products for which there is inadequate literature on safety and efficacy present a unique challenge to healthcare organizations. FDA should require pharmaceutical companies that market unapproved drugs to conduct studies and seek FDA approval, although such actions have led to price increases[40] or product shortages[41,42] as previously available generic medications were awarded patent protection by FDA.[43] Going forward, pharmacy leaders in VHA have sent the list of unapproved medications to relevant subject matter experts for clinical input. This input is currently being used to prioritize deeper discussions and potential formulary status or guidance changes for unapproved medications that (1) may have underappreciated safety concerns, (2) may be less efficacious than other approved products, and (3) lack available therapeutic alternatives. The first drug being discussed nationally is desiccated thyroid. Other healthcare systems may wish to similarly review unapproved medication purchases to ensure safety and efficacy.

Table 3. Top 25 Products Identified Within VHA System With No FDA-Approved Equivalent[a,b]

Active Pharmaceutical Ingredient(s)	Route	Potential Alternatives[c]
Sodium fluoride	Dental	Nonprescription strength
Hydrocortisone	Rectal	Nonprescription products
Benoxinate–fluorescein	Ophthalmic	Alternatives approved after study period (Dec 2017)
Tetracaine	Ophthalmic	Alternatives approved during study period (Feb 2016)
Citric acid–sodium citrate	Oral (liquid)	Potassium citrate tablets
Ephedrine	Injection	Alternatives approved during study period (Apr 2016)
Salsalate	Oral (solid)	Approved NSAIDs, acetaminophen
Aluminum chloride hexahydrate	Topical	Nonprescription strength
Hyoscyamine	Oral (solid)	Dicyclomine, ranitidine
Hydroquinone	Topical	Nonprescription strength
Epinephrine 0.1 mg/mL	Injection	Approved concentrations, as appropriate
Potassium phosphate–sodium biphosphate–sodium phosphate	Oral (solid)	
Phenobarbital	Oral (solid)	Approved antiepileptics
Urea	Topical	Nonprescription strength, Nonprescription keratolytic agents
Nitroglycerin sustained release	Oral (solid)	Nitroglycerin patches and ointments, isosorbide
Phenazopyridine	Oral (solid)	Nonprescription strength
Atropine 0.4 mg/mL, 1 mg/mL	Injection	Approved concentrations, as appropriate
Sulfacetamide–sulfur	Topical	Benzoyl peroxide and salicylic acid, prophylactic doxycycline, isotretinoin
Fluorescein strip	Ophthalmic	
Morphine	Injection	Approved strengths
Calcium gluconate	Injection	Alternatives approved after study period (May 2017)
Silver nitrate–potassium nitrate	Topical	
Belladonna–opium	Rectal	NSAIDs, phenazopyridine
Potassium bicarbonate	Oral (solid)	Approved potassium supplements
Thyroid	Oral (solid)	Levothyroxine, liothyronine

[a]VHA = Veterans Health Administration, FDA = Food and Drug Administration, NSAID = nonsteroidal antiinflammatory drug.
[b]Top 25 products overall based on number of packages purchased among National Drug Codes without an FDA-approved equivalent in the same dosage route and strength.
[c]FDA-approved prescription or nonprescription medications that are potential alternatives for the most common use(s) of the unapproved product.

The project had several limitations. Due to the study's broad scope, we were not able to assess indications for use of unapproved drugs, nor were we able to granularly evaluate safety or efficacy. To those ends, internal reviews are ongoing. The expansive scope of the project also posed other limitations. With so many agents available for consideration, decisions regarding classification of any given product were necessary. The decision to include drug-like medical devices, for instance, was intended to help capture all entities that might reasonably be considered prescription drugs. Likewise, the decision to group certain types of medications, such as multivitamins and topical wound care products, might have obscured meaningful differences in usage patterns within those classes. Follow-up studies could address this weakness via a more limited scope of inquiry, perhaps focused on analyzing unapproved medications by geographic region or most probable therapeutic role.

Conclusion

VHA purchased many unapproved prescription products in FY16 but is taking action to address use of such products in consideration of safety and efficacy data and available alternatives.

Disclosures

The authors have declared no potential conflicts of interest.

Previous affiliations

At the time of the study, Dr. Mizah was affiliated with VA Pittsburgh Healthcare System, Pittsburgh, PA. At the time of the study, Dr. Carico was affiliated with VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, and VA Center for Medication Safety, Pharmacy Benefits Management Services, Hines, IL.

Additional information

A preliminary analysis of the data reported in this article was presented as a poster at the ASHP Midyear Clinical Meeting, December 2017 in Anaheim, California. The views expressed in this article are those of the authors, and no official endorsement by the Department of Veterans Affairs or the U.S. government is intended or should be inferred.

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