

Pharmaceuticals as Environmental Contaminants: an Overview of the Science

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Why and how do drugs contaminate the environment?



***What might it all mean?
How do we prevent it?***

This talk presents only a cursory overview of some of the many science issues surrounding the topic of pharmaceuticals as environmental contaminants



A Clarification

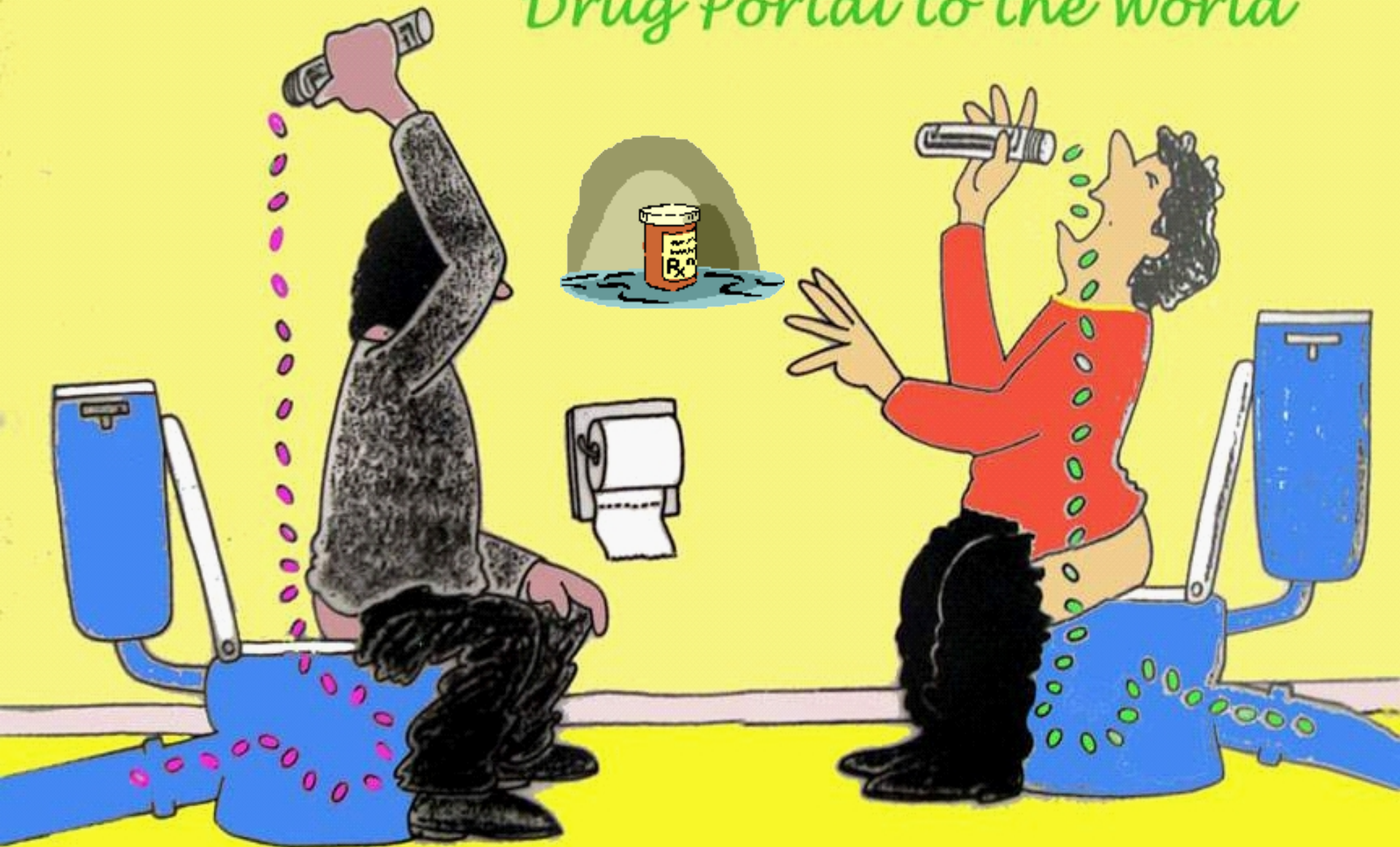
We sometimes loosely (but incorrectly) refer to **drugs, medicines, medications, or pharmaceuticals** as being the substances that contaminant the environment.

The actual environmental contaminants, however, are the *active pharmaceutical ingredients* – **APIs**.

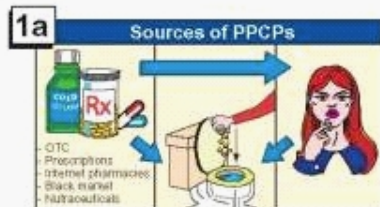
These terms are all often used interchangeably



Drug Portal to the World



adapted by Daughton from Ternes (April 2000)

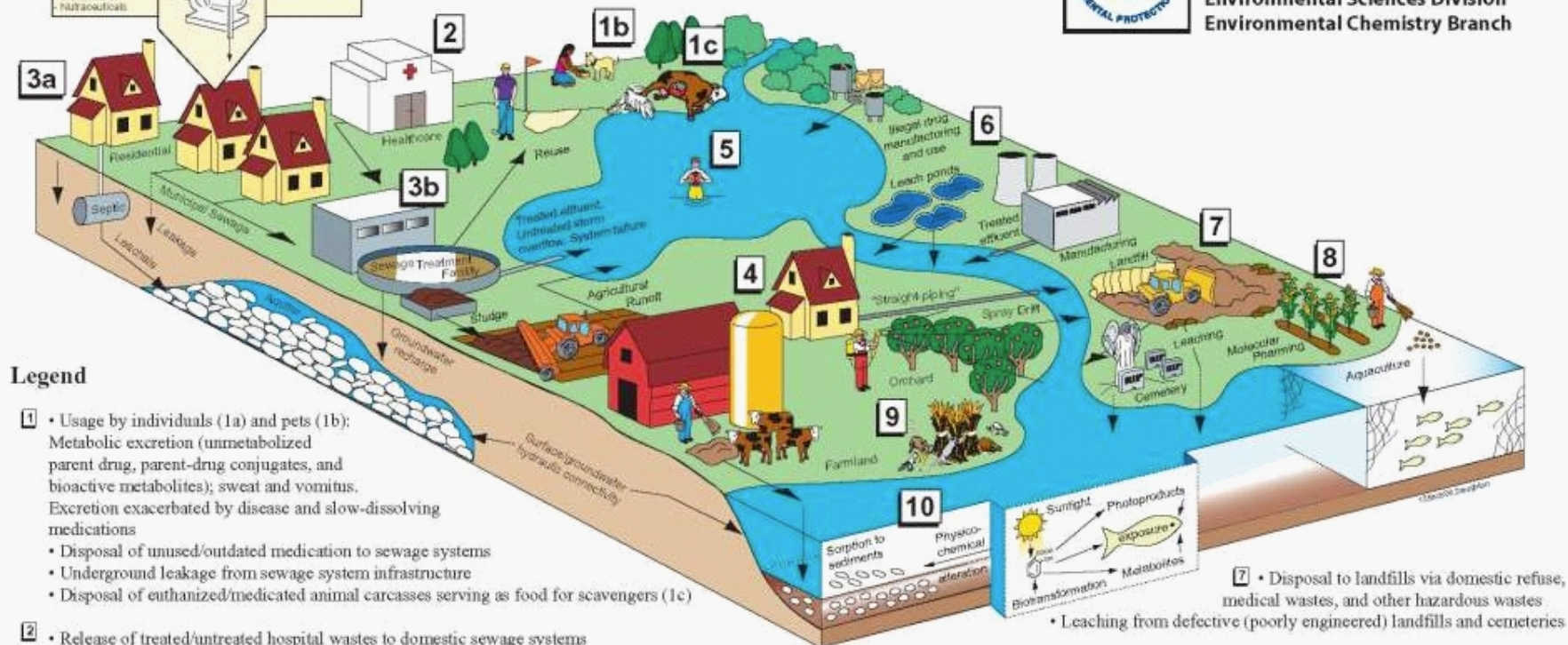


Origins and Fate of PPCPs[†] in the Environment

[†]Pharmaceuticals and Personal Care Products



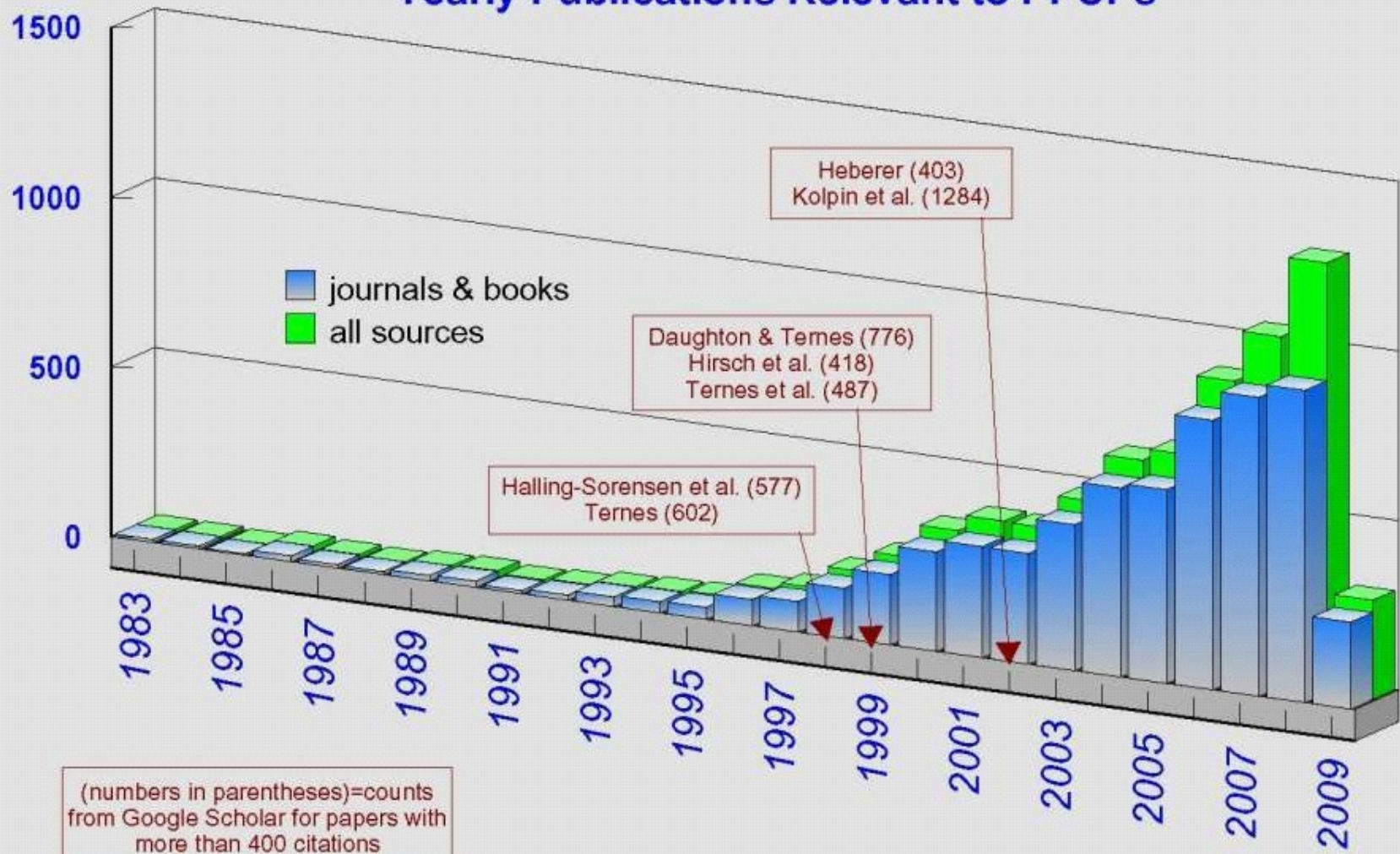
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Legend

- 1 • Usage by individuals (1a) and pets (1b): Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus. Excretion exacerbated by disease and slow-dissolving medications
 - Disposal of unused/outdated medication to sewage systems
 - Underground leakage from sewage system infrastructure
 - Disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)
- 2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus
- 3 • Release to private septic/leach fields (3a)
 - Treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b)
 - Overflow of untreated sewage from storm events and system failures directly to surface waters (3b)
- 4 • Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
 - "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
 - Release from agriculture: spray drift from tree crops (e.g., antibiotics)
 - Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)
- 5 • Direct release to open waters via washing/bathing/swimming
- 6 • Discharge of regulated/controlled industrial manufacturing waste streams
 - Disposal/release from clandestine drug labs and illicit drug usage
- 7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
 - Leaching from defective (poorly engineered) landfills and cemeteries
- 8 • Release to open waters from aquaculture (medicated feed and resulting excreta)
 - Future potential for release from molecular pharming (production of therapeutics in crops)
- 9 • Release of drugs that serve double duty as pest control agents:
 - examples: 4-aminopyridine, experimental multiple sclerosis drug → used as avicide; warfarin, anticoagulant → rat poison; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → coqui frog control
- 10 Ultimate environmental transport/fate:
 - most PPCPs eventually transported from terrestrial domain to aqueous domain
 - phototransformation (both direct and indirect reactions via UV light)
 - physicochemical alteration, degradation, and ultimate mineralization
 - volatilization (mainly certain anesthetics, fragrances)
 - some uptake by plants
 - respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

Yearly Publications Relevant to PPCPs



The Chemical Universe

We live in a chemical sea of continually changing composition – comprising both anthropogenic and naturally occurring chemical stressors.

Unlike biota, chemical pollutants have no boundaries in their global distribution –
“*everything is everywhere*,” only the concentrations vary.



The Chemical Universe

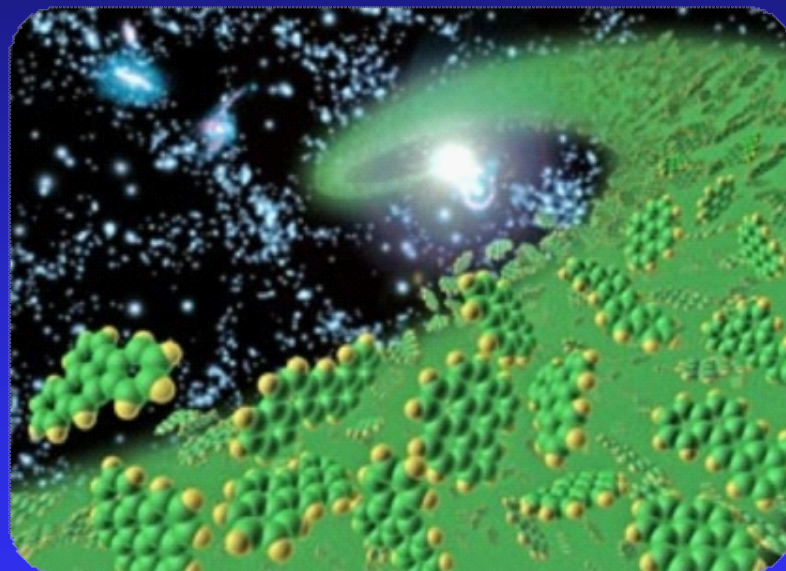
The *KNOWN* Universe

As of August 2009, over 49 million organic and inorganic substances had been assigned CAS RNs.

(indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry; excluding bio-sequences such as proteins and nucleotides:

<http://www.cas.org/expertise/cascontent/registry/regsys.html>)

- Of these millions of known chemicals, nearly 35 million were commercially available.
- Of these, fewer than a quarter million (249,000) are inventoried or regulated by numerous government bodies worldwide - - representing about 0.7% of those that are commercially available or roughly 0.5% of the known universe of chemicals.
- Approximately 12,000 new substances are added each day.



The Chemical Universe

The largest virtual chemical database yet reported comprises small drug-like molecules - - a total of over 977,000,000 structures (Blum and Reymond, 2009).

Restricted to organic molecules containing fewer than 14 atoms of C, N, O, and S (and limited types of Cl-substituted molecules). Excluded likely substituents such as F, Br, I, P, Si, metals, and most Cl.

Database represents the enormously large numbers of chemicals that could possibly be synthesized just from a very limited spectrum of types of elements and numbers of atoms.

Blum, L. C., and J.-L. Reymond. 2009. 970 Million Druglike Small Molecules for Virtual Screening in the Chemical Universe Database GDB-13. J. Am. Chem. Soc. 131 (25):8732-8733.

The Universe of Commercial APIs

- Over 21,000 formulated drug products (ingredients, strengths, and form)
- **Over 1,460 FDA-approved small-molecule APIs** (molecularly distinct); oral >800, parenteral >420; topical >270
- Over 3,200 experimental drugs

Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. "DrugBank: a knowledgebase for drugs, drug actions and drug targets." *Nucl Acids Res* 2008, 36(suppl_1):D901-906; doi:10.1093/nar/gkm958.

DrugBank PharmaBrowse web page:
<http://www.drugbank.ca/pharmabrowse#mainB>.



ALIMENTARY TRACT AND METABOLISM STOMATOLOGICAL PREPARATIONS	Dolasetron Granisetron Ondansetron LAXATIVES Lactulose Doxycycline Clotrimazole Triamcinolone Epinephrine Amphotericin B Hydrocortisone Tetracycline Natacyn Chlorhexidine Metronidazole Miconazole Dexamethasone	VITAMINS Paricalcitol Vitamin D4 (Dihydroxycholesterol) MINERAL SUPPLEMENTS Calcium Acetate Magnesium Sulfate Potassium Chloride Calcium Chloride ANABOLIC AGENTS FOR SYSTEMIC USE Oxandrolone Aspirin OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS Nitisinone Miglustat L-Carnitine Cysteamine BLOOD AND BLOOD FORMING ORGANS Balsalazide ANTITHROMBOTIC AGENTS Ticlopidine Argatroban Trepstinil Phenindione Fondaparinux sodium Warfarin Clopidogrel Tirofiban Aspirin Phenprocoumon Dipyridamole Iloprost Heparin Enoxaparin Epoprostenol ANTIHEMORRHOIDAL CS Tizanidine Tramadol Acetic Acid Diphenhydramine Acarbose Metformin Nifedipine ANTIANEMIC PREPARATIONS Hydroxocobalamin BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS Sulfamethizole Magnesium Sulfate Mannitol Potassium Chloride Chlorhexidine Neomycin	Calcium Chloride CARDIOVASCULAR SYSTEM CARDIAC THERAPY Phentermine Dofetilide Midodrine Milrinone Ranolazine Disopyramide Lidocaine Ibutilide Fumarate Mexiletine Phenylephrine Digoxin Acetyldigitoxin Metaraminol Adenosine Epinephrine Methoxamine Nitroglycerin Alprostadil Fenoldopam Dobutamine Isosorbide Dinitrate Quinidine Levosimendan Dopamine Isosorbide Mononitrate Procainamide Ibuprofen Tocainide Deslanoside Arbutamine Amiodarone Bretlyium Propafenone Flecainide Encainide ANTIHYPERLIPIDEMIC ES Reserpine Bemafibrate Nitroprusside Minoxidil Prazosin Bosentan Clonidine Doxazosin Mecamylamine Methyldopa Guafacine Deserpidine Trimethaphan Diazoxide Guanethidine Rescinnamine DIURETICS Torasemide Methyclothiazide Triamterene Spironolactone Bendroflumethiazide Metolazone	Amiloride Cyclothiazide Furosemide Eplerenone Hydroflumethiazide Indapamide Chlorothiazide Bumetanide Hydrochlorothiazide Trichlormethiazide PERIPHERAL VASODILATORS Phentolamine Nicergoline Tolazoline Pentoxifylline Phenoxybenzamine Ergoloid mesylate VASOPROTECTIVES Lidocaine Fluorometholone Betamethasone Sodium Tetracycl Sulfate Fluocinolone Acetonide Flumethasone Pivalate Plumetan Polysulfate Procaine Hydrocortisone Hydrocortamate Prednisolone Ethanol Fluocinonide Benzocaine Heparin Dexamethasone BETA BLOCKING AGENTS Esmolol Betaxolol Metoprolol Atenolol Timolol Sotalol Carteolol Propranolol Labetalol Bisoprolol Alprenolol Pindolol Carvedilol Acebutolol Nadolol CALCIUM CHANNEL BLOCKERS Isradipine Diltiazem Amlodipine Nimodipine Nisoldipine Lercanidipine Nicardipine Verapamil	Felodipine Nitrendipine Perhexiline Nifedipine Bepridil AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM Valsartan Ramipril Remikiren Olmesartan Medoxomil Fosinopril Trandolapril Benazepril Enalapril Losartan Moexipril Lisinopril Perindopril Candesartan Eprosartan Quinapril Telmisartan Irbesartan Captopril LIPID MODIFYING AGENTS Pravastatin Lovastatin Gemfibrozil Fenofibrate Clofibrate Simvastatin Colesevelam Fenofibric acid Fenofibrate Atorvastatin Fluvastatin Rosuvastatin Gemfibrozil DERMATOLOGICAL S ANTIFUNGALS FOR DERMATOLOGICAL Tolnaftate Nystatin Naftifine Haloprogin Natamycin Clorphen Terbinafine Ethan Selenium S Tioconazole Ketoconazole Butenafine	Flucytosine Miconazole Econazole Sertaconazole Ciclopirox PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS Isosorbide Dinitrate ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC. Lidocaine Procaine Triplexamine Oxybuprocaine Propylamine Diphenhydramine Benzocaine Bromodiphenhydramine Trimeprazine Chlorhexidine ANTIDOPAMINERGIC AGENTS Methoxsalen Tazarotene Etretnate ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS FOR DERMATOLOGICAL USE Idoxuridine Sulfanilamide Penciclovir Sulfadiazine Mupirocin Chloramphenicol Amikacin Sulfamethizole Oxytetracycline Demeclocycline Bacitracin Docosanol Imiquimod Tetracycline Gentamicin Metronidazole Neomycin Rifaximin CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS Diflorasone Alclometasone Fluocinonide Fluorometholone Betamethasone Desoximetasone Fluticasone Propionate	Fluocinolone Acetonide Triamcinolone Flumethasone Pivalate Hydrocortisone Mometasone Hydrocortamate Clotrolone Prednisolone Methylprednisolone Clobetasol Fluocinonide Prednicarbate Budesonide Dexamethasone ANTISEPTICS AND DISINFECTANTS Hexachlorophene Chlorhexidine Ethanol Proflavine Framycetin Chlorhexidine ANTI-ACNE PREPARATIONS Erythromycin Adapalene Fluorometholone Chloramphenicol Azelaic Acid Prednisolone Methylprednisolone Isotretinoin Clindamycin Dexamethasone OTHER DERMATOLOGICAL PREPARATIONS Pimecrolimus Minoxidil Monobenzene Magnesium Sulfate Tacrolimus Finasteride GENITO URINARY SYSTEM AND SEX HORMONES GYNCOLOGICAL ANTIINFECTIVES AND ANTISEPTICS Oxiconazole Terconazole Clotrimazole Chloramphenicol Oxytetracycline Furazolidone Butoconazole Nystatin Amphotericin B Natamycin Metronidazole	Tioconazole Ketoconazole Miconazole Econazole Candidin Ciclopirox Clindamycin OTHER GYNCOLOGICALS Cabergoline Carboprost Tromethamine Lisuride Naproxen Ritonavir Drospirenone Dienogest Tromethamine Bromocriptine SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM Diethylstilbestrol Chlortrianisene Conjugated Estrogens Etonogestrel Desogestrel Megestrol Levonorgestrel Hydrogesterone Progesterone Raloxifene Norgestrel Medroxyprogesterone Testosterone Estrone Estradiol Mifepristone Clomifene Dienestrol Norgestimate Ethinyl Estradiol Fluoxymesterone UROLOGICALS Sildenafil Trosipin chloride Morphine Solifenacin succinate Alfuzosin Darifenacin Acetohydroxamic Acid Phentolamine Tamsulosin Apomorphine Alprostadil Grepafloxacin Vardenafil Tolterodine Oxybutynin Dimethyl sulfoxide Papaverine Dutasteride Flavoxate	Terazosin Calcium Chloride Finasteride SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND HORMONES AND ANALOGUES Gonadorelin Nafarelin Carbetocin CORTICOSTEROIDS FOR SYSTEMIC USE Triamcinolone Prednisone Fludrocortisone Hydrocortisone Prednisolone Rimexolone Methylprednisolone Trilostane Dexamethasone THYROID THERAPY Liothyronine Carbamazole Levothyroxine Propylthiouracil CALCIUM HOMEOSTASIS Cinacalcet ANTIINFECTIVES FOR SYSTEMIC USE ANTIBACTERIALS FOR SYSTEMIC USE Erythromycin Azithromycin Moxifloxacin Cefotiam Doxycycline Lymecycline Sulfanilamide Cefmenoxime Cefmetazole Flucloxacillin Ertapenem Piperacillin Aztreonam Sulfadiazine Grepafloxacin Ampicillin Penicillin V Cefpiramide Ceftazidime Trimethoprim Chloramphenicol Loracarbef
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A listing of nearly all of the FDA approved APIs 711,460

Clomocycline	Fluconazole	Piprobroman	Aminoglutethimide	Ibuprofen	Anileridine	ANTI-PARKINSON	Zaleplon	Bupropion	Lidocaine
Enoxacin	Anidulafungin	Cladribine	Progesterone	Dimethyl sulfoxide	Mepivacaine	DRUGS	Acetophenazine		Bacitracin
Amikacin	Caspofungin	Anagrelide	Flutamide		Levobupivacaine	Benzotropine	Melatonin	ANTIPARASITIC	Dyclonine
Dicloxacillin	Voriconazole	Carmustine	Toremifene	MUSCLE	Methoxyflurane	Cabergoline	Pimozide	PRODUCTS,	Chlorhexidine
Pefloxacin	Amphotericin B	RELAXANTS	Medroxyprogesterone	RELAXANTS	Benzocaine	Ropinirole	Methypyrylon	INSECTICIDES AND	Cocaine
Cefotaxime	Ketconazole	Bleomycin	Nilutamide	Baclofen	Halothane	Morphine	Zopiclone	REPELLENTS	Neomycin
Vancomycin	Flucytosine	Chlorambucil	Tamoxifen	Chlorzoxazone	Flucorprocaine	Tolcapone	Estazolam	ANTIPROTOZOALS	Benzocaine
Cefdinir	Miconazole	Raltitrexed	Estradiol	Carisoprodol	Desflurane	Metixene	Quetiapine	Pyrimethamine	
Ciprofloxacin	Micafungin	Mitomycin	Fulvestrant	Metocurine Iodide	Ketamine	Trihexyphenidyl	Aripiprazole	DRUGS FOR	
Cephalexin	Itraconazole	Bexarotene	Exemestane	Methocarbamol	Sevoflurane	Procyclidine	Chlorprothixene	OBSTRUCTIVE	
Sulfamethizole		Vindesine	Letrozole	Gallamine Triethiodide		Pramipexole		Chloroquine	AIRWAY DISEASES
Carbenicillin	ANTIMYCOBACTERIALS	Gefitinib	Bicalutamide	Cisatracurium Besylate	ANALGESICS	Entacapone	PSYCHOANALEPTICS	Amodiaquine	Flunisolide
Oxytetracycline	ALS	Thioguanine	Anastrozole	Tizanidine	Tramadol	Atropine	S	Pentamidine	Theophylline
Linezolid	Aminosalicylic Acid	Vinorelbine		Rocuronium	Eletriptan	Apomorphine	Fluvoxamine	Tinidazole	Ipratropium
Demeclocycline	Dapsone	Valrubicin	IMMUNOSUPPRESSIVE AGENTS	Atracurium	Methysergide	Biperiden	Amphetamine	Metronidazole	Beclomethasone
Cefixime	Cycloserine	Streptozocin		Cyclobenzaprine	Morphine	Amantadine	Caffeine	Primaquine	Betamethasone
Tobramycin	Capreomycin sulfate	Gemcitabine	Methotrexate	Doxacurium chloride	Zolmitriptan	Selegiline	Citalopram	Atovaquone	Montelukast
Trovafoxacin	Ethambutol	Teniposide	Tacrolimus	Orphenadrine	Acetaminophen	Orphenadrine	Reboxetine	Progumil	Zafirlukast
Nitrofurantoin	Pyrazinamide	Epirubicin	Sirolimus	Chlormezanone	Codeine	Pergolide	Venlafaxine	Trimetrexate	Fluticasone Propionate
Oxacillin	Ethionamide	Celecoxib	Azathioprine	Tubocurarine	Dihydroergotamine	Bromocriptine	Atomoxetine	Halofantrine	Piperazine
Procaine	Rifabutin	Altretamine	Mycophenolic acid	Dantrolene	Hydromorphone	Levodopa	Amitriptyline		Triamcinolone
Hetacillin	Clofazimine	Cisplatin	Thalidomide	Mivacurium	Methadone		Protriptyline	ANTHELMINTICS	Dyphylline
Tetracycline	Isoniazid	Alitretinoin	Leflunomide		Oxycodone		Mirtazapine	Albendazole	Epinephrine
Meropenem	Rifapentine	Oxaliplatin		ANTIGOUT	Clonidine		Tacrine	Piperazine	Nedocromil
Roxithromycin		Erlotinib	MUSCULO-SKELETAL SYSTEM	PREPARATIONS	Lisuride		Methylphenidate	Ivermectin	Mometasone
Nalidixic Acid	ANTIVIRALS FOR SYSTEMIC USE	Cyclophosphamide	ANTIINFLAMMATORY AND	Allopurinol	Butorphanol	Temazepam	Imipramine	Mebendazole	Terbutaline
Polymyxin B Sulfate		Vincristine		Probenecid	Propoxyphene	Ziprasidone	Fluoxetine	Diethylcarbamazine	Bitolterol Mesylate
Gentamicin		Vidarabine	ANTITUMORIC	Sulfapyrazone	Pentazocine	Talbutal	Duloxetine	Levamisole	Salmeterol
Colistin	Oseltamivir	Pentostatin	PRODUCTS		Sumatriptan	Pentobarbital	Nortriptyline	Praziquantel	Formoterol
Cinoxacin	Nelfinavir	Methotrexate		DRUGS FOR TREATMENT OF BONE DISEASES	Ergotamine	Olanzapine	Amoxapine	Oxamniquine	Amexanox
Fosfomycin	Indinavir	Vinblastine			Fentanyl	Clobazam	Trazodone		Budesonide
Cefaclor	Nevirapine	Imatinib			Nalbuphine	Clozapine	Galantamine	ECTOPARASITICIDES, INCL.	Aminophylline
Sulapyridine	Idoxuridine	Clofarabine			Diffunisal	Meprobamate	Paroxetine	SCABICIDES, INSECTICIDES AND REPELLENTS	PREPARATIONS
Tinidazole	Penciclovir	Pemetrexed			Almotriptan	Sulpiride	Trimipramine		Morphine
Metronidazole	Tenofovir	Mitotane			Buprenorphine	Eszopiclone	Modafinil		Codeine
Spectinomycin	Cidofovir	Daunorubicin			Aspirin	Alprazolam	Tranylcypromine		Methadone
Ceforanide	Famciclovir	Porfimer			Naratriptan	Loxapine	Phenelzine		Dextromethorphan
Mezlocillin	Entecavir	Irinotecan			Rizatriptan	Minaprine	Minaprine		Benzonatate
Dirithromycin	Rimantadine	Etoposide			Frovatriptan	Secobarbital	Donepezil		Guafenesin
Netilmicin	Zidovudine	Dacarbazine			Dezocine	Promazine	Maprotiline		Hydrocodone
Telithromycin	Ritonavir	Sulindac		OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM		Zolpidem	Rivastigmine	RESPIRATORY SYSTEM NASAL PREPARATIONS	ANTIHISTAMINES FOR SYSTEMIC USE
Lomefloxacin	Foscarnet	Aminolevulinic acid				Prochlorperazine	Memantine		Clemastine
Neomycin	Zanamivir	Caboplatin				Droperidol	Sertraline		Cetirizine
Sulfamethoxazole	Efavirenz	Dactinomycin				Methohexital	Doxepin		Terfenadine
Minocycline	Stavudine	Cytarabine				Chlordiazepoxide	Nefazodone		Bucilizine
Gatifloxacin	Amphenavir	Methyl aminolevulinic acid				Valproic Acid	Desipramine		Doxylamine
Penicillin G	Delavirdine	Doxorubicin				Trimethadione	Moclobemide		Thiethylperazine
Norfloxacin	Lamivudine	Busulfan				Metharbital	Escitalopram		Dexbrompheniramine
Amoxicillin	Adefovir Dipivoxil	Topotecan				Mephentoin	Pemoline		Triprolidine
Azlocillin	Ribavirin	Mercaptopurine				Lamotrigine	Mupirocin		Cyproheptadine
Cefditoren Pivoxil	Emtricitabine	Melphalan				Carbamazepine	Betamethasone		Loratadine
Streptomycin	Didanosine	Fludarabine				Thiopental	Framycetin		Astemizole
Cefuroxime	Tipranavir	Capecitabine				Fluphenazine	Fluticasone Propionate		Mometasone
Levofloxacin	Zalcitabine	Procabazine				Clorazepate	Fluticasone Propionate		Pseudoephedrine
Cefadroxil	Ganciclovir	Arsenic trioxide				Thioridazine	Fluticasone Propionate		Cinnarizine
Cloxacillin	Abacavir	Idarubicin				Midazolam	Betamethasone		Oxymetazoline
Cefprozil	Atazanavir	Ifosfamide				Flurazepam	Framycetin		Naltrexone
Gemifloxacin	Saquinavir	Estramustine				Risperidone	Fluticasone Propionate		Riluzole
Ofloxacin		Mitoxantrone				Coprolamine	Fluticasone Propionate		Disulfiram
Kanamycin	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Lomustine				Propiomazine	Fluticasone Propionate		Buprenorphine
Clindamycin		Paclitaxel				Halazepam	Fluticasone Propionate		Bethanechol
Sparfloxacin	IMMUNOMODULATING AGENTS	Docetaxel				Diazepam	Fluticasone Propionate		Pilocarpine
Clarithromycin	ANTINEOPLASTIC AGENTS					Clonazepam	Fluticasone Propionate		Amibenonium
Ceftriaxone		ENDOCRINE THERAPY				Vigabatrin	Fluticasone Propionate		
		Diethylstilbestrol				Phenacemide	Fluticasone Propionate		
		Megestrol				Levetiracetam	Fluticasone Propionate		
						Mesoridazine	Fluticasone Propionate		

Azelastine	Olopatadine	Polymyxin B Sulfate	Aminohippurate	Pivalate	Lapatinib	Pivmecillinam
Promethazine	Polymyxin B Sulfate	Gentamicin	Aminophenazone	Dexmedetomidine	Lenalidomide	Podofilox
Mequitazine	Gentamicin	Prednisolone	Amobarbital	Dibucaine	Leucovorin	Posaconazole
Diphenhydramine	Tropicamide	Chlorhexidine	Amyl Nitrite	Dicumarol	Levallorphan	Practolol
Chlorpheniramine	Acetazolamide	Neomycin	Anisindione	Dicyclomine	Levomethadyl Acetate	Pranlukast
Diphenylpyraline	Natamycin	Ofloxacin	Anisotropine	Digitoxin	Levorphanol	Probutol
Cyclizine	Prednisolone	Dexamethasone	Methylbromide	Dimenhydrinate	Lincomycin	Procatenol
Bromodiphenhydramine	Dorzolamide		Ardeparin	Dimethylthiambutene	Lisdexamfetamine	Proprietaryzine
Trimeprazine	Loteprednol Etabonate	VARIOUS ALL	Arformoterol	Diphenidol	Lopinavir	Quinacrine
	Chlorhexidine	OTHER	Azacitidine	Divalproex sodium	Lubiprostone	Ramelteon
OTHER	Oxybuprocaine	THERAPEUTIC	Bacampicillin	Dromostanolone	Lumiracoxib	Rasagiline
RESPIRATORY	Rimexolone	PRODUCTS	Bambuterol	Drospirenone	Marimastat	Retapamulin
SYSTEM PRODUCTS	Bimatoprost	Hydroxocobalamin	Bentoquatam	Echothiophate Iodide	Mechlorethamine	Ridogrel
Nitric Oxide	Cocaine	Dexrazoxane	Benzphetamine	Edrophonium	Meclizine	Rifampin
Doxapram	Ketotifen Fumarate	Sevelamer	Benzquinamide	Enprofylline	Menthol	Rosoxacin
	Oxymetazoline	Pralidoxime	Benzthiazide	Ergonovine	Meperidine	Salbutamol
SENSORY ORGANS	Demecarium bromide	Deferoxamine	Benzylpenicilloyl	Erythrityl Tetranitrate	Mephentermine	Salicyclic acid
OPHTHALMOLOGIC	Netilmicin	Ethanol	Polylysine	Ethacrynic acid	Mesalazine	Salsalate
ALS	Apraclonidine	Edetic Acid	Bevantolol	Ethinamate	Metaxalone	Sitagliptin
Vidarabine	Azelastine	Physostigmine	Bezafibrate	Ethiodized oil	Methacycline	Sodium lauryl sulfate
Betaxolol	Lomefloxacin	Diazoxide	Bromfenac	Ethopropazine	Methimazole	Sorafenib
Erythromycin	Cyclopentolate	Amifostine	Bufotenine	Ethoxzolamide	Methotrimeprazine	Succinylcholine
Alclometasone	Physostigmine	Naloxone	Butabarbital	Ethynodiol Diacetate	Methylgonovine	Sulfametopyrazine
Idoxuridine	Nandrolone	Flumazenil	Butalbital	Etoricoxib	Methylphenobarbital	Sulfisoxazole
Medrysone	Neomycin	Fomepizole	Calcium Gluceptate	Fenoterol	Meticillin	Sulfoxone
Lidocaine	Ganciclovir		Candoxatril	Floxuridine	Metyrosine	Sunitinib
Travoprost	Gatifloxacin	DIAGNOSTIC	Carbidopa	Flunitrazepam	Mibefradil	Telbivudine
Morphine	Penicillin G	AGENTS	Carphenazine	Flupenthixol	Mimosine	Temafloxacin
Dapiprazole	Norfloxacin	Pentagastrin	Carprofen	Flurandrenolide	Mitiglinide	Testolactone
Fluorometholone	Streptomycin	Betazole	Cefalotin	Forasartan	Molindone	Tetrahydrobiopterin
Timolol	Emedastine	Ceruletide	Cefazolin	Fosphenytoin	Moricizine	Thiabendazole
Phenylephrine	Pilocarpine	Bentriomide	Cefepime	Gamma Hydroxybutyric Acid	Mycophenolate mofetil	Thiamylal
Carbachol	Levocabastine	Inulin	Cefotetan	Gentian Violet	Nafcillin	Thiopropazone
Ampicillin	Heparin	Gonadorelin	Cefpodoxime	Glibenclamide	Nelarabine	Thiothixene
Famciclovir	Levofloxacin	Magnesium Sulfate	Cefibuten	Gliquidone	Neostigmine	Tiaprofenic acid
Trifluridine	Dichlorphenamide	Histamine Phosphate	Cephaloglycin	Glutethimide	Nitazoxanide	Ticarcillin
Betamethasone	Ofloxacin	Metyrapone	Cephapirin	Glycodiazine	Nitrazepam	Tigecycline
Chloramphenicol	Guanethidine	Tolbutamide	Cerulenin	Glycopyrrolate	Nitrofurazone	Trimethobenzamide
Dipivefrin	Kanamycin		Cevimeline	Guanabenz	Norepinephrine	Troleandomycin
Framycetin	Brinzolamide	CONTRAST MEDIA	Chlormerodrin	Guanadrel Sulfate	Norethindrone	Uracil mustard
Verteporfin	Levobunolol	Gadodiamide	Chloroxine	Halobetasol Propionate	Novobiocin	Valaciclovir
Methylscopolamine	Metipranolol	Diatrizoate	Chlorthalidone	Hesperetin	Olsalazine	Valganciclovir
Ketorolac	Dexamethasone	Gadoversetamide	Cilastatin	Hexafluorenum	Omapatrilat	Varenicline
Amikacin		Gadoteridol	Cilostazol	Bromide	Orciprenaline	Yohimbine
Brimonidine	OTOLOGICALS	Gadobenate	Cinalukast	Hexobarbital	Oubain	Zileuton
Carteolol	Lidocaine	Dimeglumine	Cinolazepam	Hydroxyurea	Oxprenolol	Zuclopenthixol
Ciprofloxacin	Betamethasone	Gadopentetate	Clavulanate	Hexylcaine	Oxybenzone	
Piroxicam	Chloramphenicol	dimeglumine	Clenbuterol	Hydralazine	Oxymorphone	
Atropine	Hydrocortisone		Clidinium	Hydroxychloroquine	Paliperidone	
Clonidine	Tetracycline	DIAGNOSTIC	Colchicine	Hydroxypropyl cellulose	Palonosetron	
Sulfamethizole	Polymyxin B Sulfate	RADIOPHARMACEU	Colistimethate	Hydroxystilbamidine	Pamidronate	
Diclofenac	Gentamicin	TICALS	Conivaptan	Isethionate	Paramethasone	
Oxytetracycline	Prednisolone	Succimer	Cromoglicate	Hydroxyurea	Pargyline	
Triamcinolone	Chlorhexidine		Crotamiton	Idocextrin	Paromomycin	
Sulfacetamide	Cocaine	UNCLASSIFIED	Cryptenamine	Imipenem	Pemirolast	
Latanoprost	Neomycin	3-Methylthiofentanyl	Cyclacillin	Indecainide	Pentolinium	
Epinephrine	Miconazole	5-Methoxy-N,N-diisopropyltryptamine	Cyrimine	Indomethacin	Perflutren	
Tobramycin	Dexamethasone		Danazol	Iodixanol	Phenazopyridine	
Fluorescein		Acenocoumarol	Darunavir	Iohexol	Phenindamine	
Methazolamide	OPHTHALMOLOGIC	Acepromazine	Dasatinib	Iophendylate	Pheniramine	
Flurbiprofen	AL AND	Aceprometazine	Decamethonium	Iron Dextran	Phenmetrazine	
Nedocromil	OTOLOGICAL	Aciclovir	Decitabine	Isoetharine	Phenobarbital	
Procaine	PREPARATIONS	Aliskiren	Deferasirox	Isoflurophate	Phytonadione	
Hydrocortisone		Almitrine	Delta1-	Isopropamide	Picrotoxin	
Scopolamine	Chloramphenicol	Alseroxylon	dihydrotestosterone	Isoproterenol	Pipotiazine	
Epinastine	Ciprofloxacin	Alverine	Desonide	Josamycin	Pirbuterol	
Tetracycline	Tetracycline	Amdinocillin	Desoxycorticosterone		Pivampicillin	

200 Top-Selling Prescribed Drugs (2006)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160
161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180
181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200

Routes of Entry to the Environment for APIs

APIs are released to the environment by two primary routes:

sewerage:

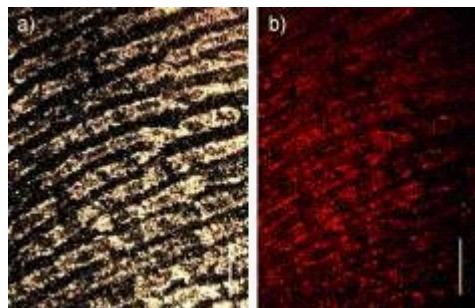
- excretion (as a function of pharmacokinetics)
- bathing (topically applied drugs and residues excreted via sweat)
- disposal to drains

trash:

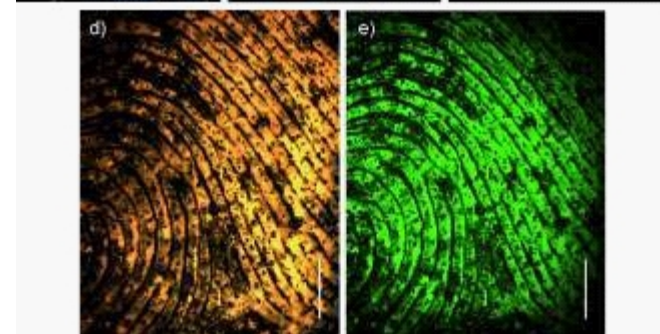
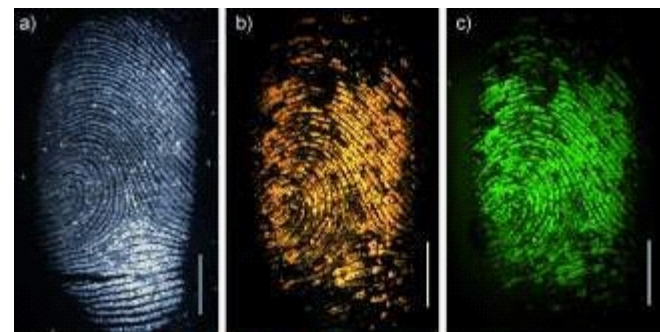
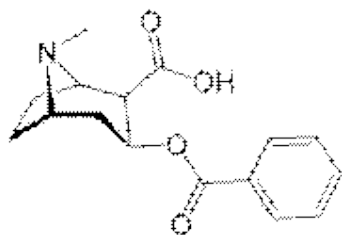
- discarding unwanted new medications
- as well as used delivery devices or containers with residuals



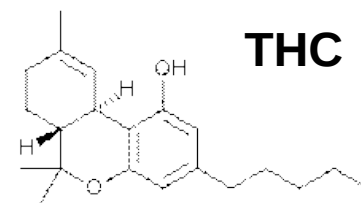
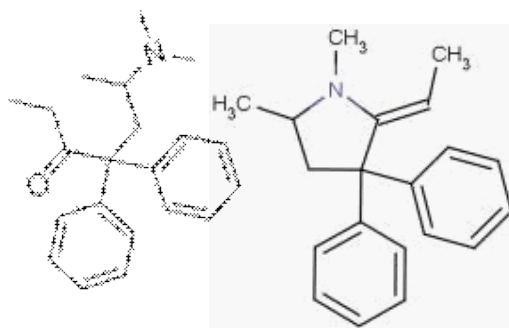
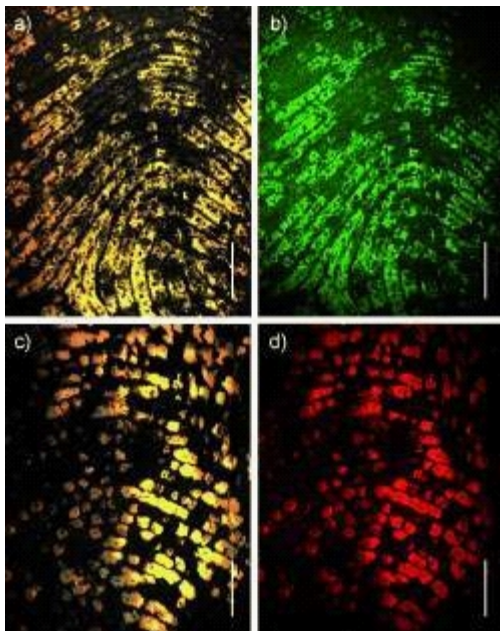
Fingerprints as contributors of environmental contaminants



benzoylecgonine



methadone & EDDP



benzoylecgonine (major cocaine metabolite)

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (major methadone metabolite)

THC: Δ^9 -tetrahydrocannabinol (main psychoactive of marijuana)

Hazarika P, Jickells SM, Wolff K, Russell DA (2008) Imaging of Latent Fingerprints through the Detection of Drugs and Metabolites. *Angew Chem Int Ed* 47:10167-10170.

Sewage Treatment & Natural Attenuation

- Efficiency of API removal is highly variable – ranging from nearly complete to almost nil as a function of the API.
- Concentrations in treated sewage often range from 1-100 ng/L.
- “Removal” does not necessarily equate with “destruction” or with elimination of toxicity.
 - Parent (unchanged) APIs can partition to solid sludge.
 - Bioactive transformation products can be created.
 - API conjugates serve as hidden reservoirs of parent API.



Emerging Challenges Posed by Analytical Chemistry

- Increasingly advanced methods of analysis allow peering into the shadows of chemical space with ever-greater magnification and clarity.
- In last 10 years, APIs in the environment can be detected below concentrations of 1 part-per-trillion (ng/L) - or the pM range.
- Ever-lower detection limits pose increasingly greater challenges for assessing, communicating, and ameliorating ever-diminishing risks.



Toxicity of Complex Environmental Mixtures: Poses Major Unanswered Questions



**Significance of long-term exposure to
multiple APIs each present at levels
below known effect levels**

While the focus of science has been on the potential for aquatic effects, the public and press primarily have been concerned with APIs in drinking water



Effects on Aquatic Organisms: Cause for Concern

- “Pseudo-persistence”
 - Continuous, multigenerational exposure
- Endocrine disruption (sub-ppb/ppt levels)
 - alterations to sexual differentiation
 - feminization; intersex
 - reproduction and growth impairments
 - Canadian lake study – EE2
 - subtle, behavioral effects - antidepressants
- More questions than answers



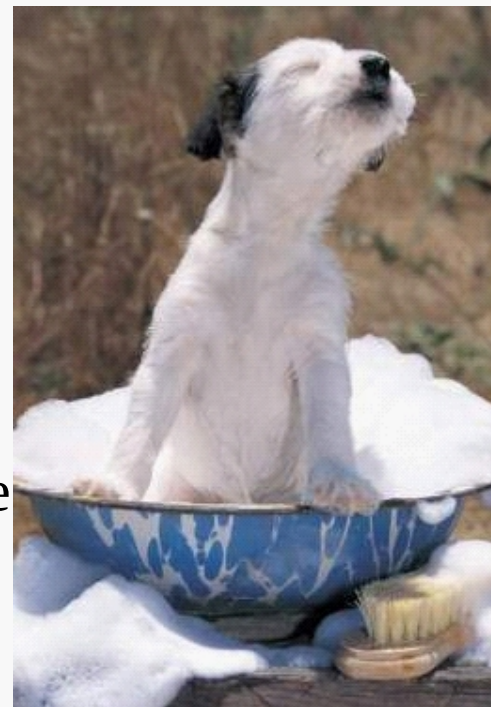
The Potential for Human Health Effects

- Human exposure to APIs recycled from the environment via potable water is limited
- Extremely low concentrations (< 10 ng/L)
- Many APIs in source waters are removed by treatment
- Toxicological research restricted to *in vitro* studies and very limited epidemiological data.
- Concern focused primarily on vulnerable windows of exposure (e.g., fetal exposure) or to contraindicated APIs.
- Therapeutic levels are irrelevant (different mechanisms of action at ultra-low levels)



Significance of Disposal versus Excretion and Bathing

- **Excretion:** continual low-level contributions of wide spectrum of APIs from multitudes of people
- **Bathing:** releases fewer types of APIs (medications applied directly to the skin and excreted via sweat) but at higher levels
- **Disposal:** acute but transient and episodic contributions from fewer people
 - Disposal is the only route that is most directly amenable to pollution prevention or source control measures
 - Proper disposal is greatly complicated by the conflict between the need to protect public safety and the need to minimize aquatic (and terrestrial) exposure



Major Unknown

- **What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?**
 - No studies provided objective data from well-defined populations to support any type of conclusion
 - Data are needed on the types, quantities, and frequencies with which drugs accumulate and are disposed of as household waste



Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-Month Period: Categorized by Therapeutic Class

ATC Code	ATC Main Group	Quantity (mg) disposed	#of APIs	% of Total
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Anti-infectives	5,608,735	45	10.4
M	Musculoskeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
TOTAL		53,945,042	367	

Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, 34(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available:

<http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf>

Drug Disposal: Major Unknowns



- Unknown: what types or quantities of APIs enter the environment via disposal.
- More importantly, it is not known what percentage of each API's environmental loading is contributed by disposal.
- Disposal could be significant for certain APIs and insignificant for others.
- This means that conscientious control of disposal may not lead to any detectable change in the environmental occurrence of many (or most) APIs.

Drug Disposal: Major Unknowns

- Significance of antibiotic residues in environment with respect to evolution of pathogen resistance
- Portion of human poisonings resulting from accidental ingestion and abuse of diverted drugs that are stored or disposed imprudently
- Prevention of diversion and human poisonings may be the more important driver for prudent disposal.



Drug Disposal: Major Objectives

- An emphasis regarding disposal needs to be on protecting humans, pets, and wildlife from unintended acute exposures as a result of imprudent storage, stockpiling, or disposal of unwanted medications.
- Critical that guidance for disposal of drugs not jeopardize protection of human (or ecological) health.
- The ultimate objective, however, needs to be on reducing or eliminating the incidence of unwanted medications to begin with.



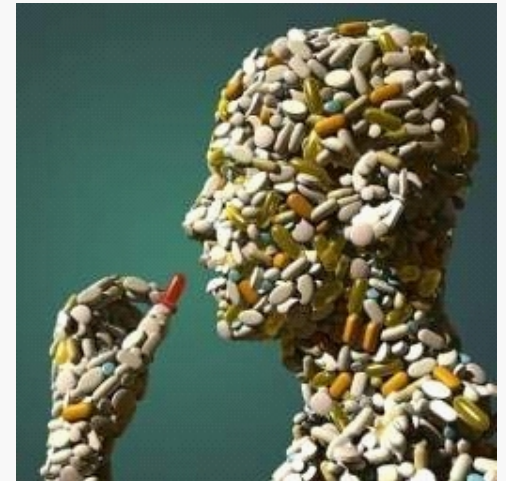
Ultimate Objective: *No Leftover Drugs*

long-term focus should not be how to
properly dispose of drugs,
but rather *how to minimize, and
ultimately eliminate the creation of
drug waste*



Reducing Leftover Drugs

- **Actions can be directed at improvements to any part of the life cycle of medications**, such as those spanning the vast, complex chain beginning with design/discovery, manufacturing, packaging, and advertising, and proceeding to prescribing (as also modified by practices of healthcare insurers) and dispensing, and ending with whether the medications are eventually consumed or used by the consumer.
- **Actions can be directed** not just at prudent alternatives for disposal, but **also (and more significantly) to reducing the contributions from excretion and bathing.**



Actions to reduce APIs in the environment and protect human health & safety

- Unit dosing
- Trial scripts
- Reduce polypharmacy
- Samples and donations
- Increased monitoring of patient
- Implement practice of concordance
- Personalized medicine (e.g., lower doses)
- Reduce incentives for excessive purchasing
- Low-quantity packaging of OTC medications
- Lower doses via non-racemic or deuterated APIs
- Prescribers to account for possible environmental impact
- Widespread implementation of sustainable take-back programs



Stewardship and Pollution Prevention

Disposal control vs. Usage control:

two basic approaches for reducing the entry of APIs to the environment

- **Disposal control:** prudent and environmentally sound engineered practices for disposal of unwanted medications.
- **Usage control:** prudent healthcare practices to minimize or optimize prescribing and dispensing of medications by eliminating unnecessary or imprudent customs.
- Significantly, **usage control perhaps has greater potential for reducing overall entry of APIs to the environment.** It can eliminate the need for disposal PLUS also minimize the residues that would otherwise be released by excretion and bathing.

Collateral Benefits to Pollution Prevention & Usage Control

In addition to reducing environmental contamination by APIs, prudent stewardship actions aimed at ensuring prudent, efficacious usage of medications might also:

- **lessen healthcare costs** (via more effective treatment, reduced purchase costs, fewer prescribing/dispensing errors)
- **improve therapeutic endpoints and healthcare outcomes** (via better patient adherence/compliance)
- **reduce morbidity and mortality** caused by poisonings of infants, children, adults, pets, and sometimes wildlife by unused stored drugs or by drugs improperly disposed in trash.

Pharm*Ecovigilance*

Conventional pharmacovigilance expanded beyond conventional focus on adverse drug reactions (ADRs) to encompass environmental concerns

Unify the parallel but interconnected needs for protecting both human and ecological health

***Drug Disposal and Stewardship:
Ramifications for the Environment
and Human Health***



EPA publications on this topic:

<http://www.epa.gov/ppcp/projects/disposal.html>



Questions

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