Review article

Closing the loop: An integrative framework for managing unwanted pharmaceuticals during COVID-19 and beyond

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Abstract. Improved healthcare and an aging global population have exacerbated demand for pharmaceuticals. During the novel coronavirus disease (COVID-19) pandemic, individuals are either prescribed with excess medications or proactively stockpile over-the-counter drugs to ensure preparedness or under panic buying, which may have left an unprecedent quantity of expired and excess pharmaceuticals in households around the globe. Unwanted household pharmaceuticals are normally collected and incinerated in centralized facilities. This approach, however, relies on bulk collections through drug take-back programs that are held regularly in communities and voluntary actions by drug owners. During COVID-19, these programs have been impacted by lockdowns and the shortage of resources under constant prioritization efforts, while excess and unwanted pharmaceuticals are left to expire in households. Inappropriate disposal of these pharmaceuticals, given their sheer volume and bioactivities, pose a significant threat to the ecosystem and public health. Meanwhile, many pharmaceuticals are in short supply as production capacities are constrained by the ongoing pandemic. The U.S. Food and Drug Administration reported that under normal storage conditions, active pharmaceutical ingredients (APIs) in drugs generally remain intact and potent long after their expiring dates (as long as 15 years). Further, most synthetic drugs have a simple matrix with few ingredients and good environmental stability. So far, there is a lack of effective and sustainable strategies to manage unwanted pharmaceuticals in an epidemic or pandemic scenario. The key to address this unmet demand is to enable user-based submission of drugs and information, with machine-readable codes for automatic sorting and fine-categorization, and explore existing techniques for the recovery of APIs from unwanted pharmaceuticals for reuse. By utilizing the existing Internet and logistics infrastructure, this article proposes a new strategy for managing unwanted household pharmaceuticals where owners—as opposed to staff in centralized waste management facilities—sort their unwanted pharmaceuticals and submit information online where the system auto-generates free coded mailing labels to separate opened and unused pharmaceuticals as well as expired and non-expiring varieties. These will be shipped to centralized sorting facilities where unopened pharmaceuticals will be further sorted by code scanning and categorization based on their active ingredients, expiring dates, and forms (tablets, capsules, gels). Depending on their formulation, fine-sorted drug varieties will be ready for API extraction, returned to manufacturers for de-formulation and reuse, or re-distributed to other patients in need, thereby closing the loop in managing the flow of pharmaceuticals. Such an integrated policy and technology framework will not only reduce the entry loads of bioactive pharmaceuticals into the environment, but alleviate the shortage and costs of pharmaceuticals and raw ingredients by tapping into the vast resource left from the current pandemic and beyond.

Keywords: Medicine; drug; recycle; recovery; pandemic; coronavirus

1. Introduction

An aging global population and rising health-seeking awareness have resulted in the long-term growth of pharmaceutical use over the past few decades (Kahsay et al. 2020). Every year, there is an enormous quantity of pharmaceuticals left unused or expired after being dispensed to patients due to patient incompliance, over-prescription, improvements on medical conditions and, in some cases, the decease of patients (Insani et al. 2020). In the United States alone, patients waste more than $1 billion worth of prescription drugs every year by disposing them as general household wastes or pilling them up in medical cabinets at home (Opar et al. 2006). In the United Kingdom, the equivalent figure is about £300m a year (Trueman et al. 2010). The outbreak of the coronavirus disease (COVID-19) pandemic since 2019 has increased the demand for pharmaceuticals, with large quantities of expired, unused, and unwanted medications pile up in households (Dai et al. 2021). The uncertainty of COVID-19 caused an anticipatory surge of purchases of medications around the world, driving demand to an unprecedented level. In China, people rushed to local pharmacies and hoarded Lianhua Qingwen (Lotus Plague Clearing) capsules, a traditional Chinese medicine, after hearing reports that the medicine showed effects in treating COVID-19 symptoms (NATCM 2020; Zeng et al. 2020). Yiling Pharmaceuticals, a manufacturer of Chinese traditional medicines, reported that sales of Lianhua Qingwen capsules increased by nearly 150% in 2020 compared with the previous year, driven by the surging demand (SYP 2020). In 2020, sales of pharmaceuticals in the U.S. totaled over 530 billion, representing an overall growth of 8% compared with the equivalent figure in 2019 (Statista 2022a). In the meantime, some manufacturing plants were shut down to prevent the spread of COVID-19, resulting in a persisting shortage of some pharmaceuticals in some countries and regions (US Pharmacist 2021).

Current practices of household disposal of expired and unwanted pharmaceuticals are unsustainable and even pose looming threats for the environmental and public health. A memorandum was released in September 2012 by the U.S. Environment Protection Agency (EPA) which recommended incineration as the preferred method of disposal for unwanted pharmaceuticals collected from households (EPA 2022). EPA encourages the public to take advantage of its drug take-back programs that accept both prescription and over-the-counter drugs, as these offer a safe, convenient, and environmentally-conscious way to dispose of unwanted medicines. Owners could drop off their expired, unused, opened, or other unwanted drugs at a designated drug take-back site (FDA 2020a), such as a local pharmacy, healthcare provider, or law enforcement agency (e.g., police station) (EPA 2022). The U.S. Drug Enforcement Administration (DEA) sponsors the National Prescription Drug Take Back Day, offering about 11,000 collection sites in communities nationwide. As of May 2021, DEA collected 14,524,391 pounds, or nearly 6,600 metric tons, of unused, expired, and unwanted medications along with its law enforcement partners since the inception of the National Prescription Drug Take Back Initiative in 2010 (DEA 2021). These collection programs, however, were deterred in 2020 due to the risks of viral transmission in public settings (Chen et al. 2021a; He and Han, 2021; Wang et al. 2021). The National Prescription Drug Take Back Day scheduled on 25 April 2020 was canceled due to COVID-19 (DEA 2022). It collected 985,392 pounds (447 metric tons) of medications across the country in 2020, which was about half of the quantity collected in 2019 (826 tons) (DEA 2022).

Owners are faced with two options if a drug take-back program is not available. If the unwanted medication is on the 'Flush List', a list of pharmaceutical products published by U.S. Food and Drug Administration (FDA)

containing ten opioids and three non-opioid active pharmaceutical ingredients (APIs) (**Table 1**), owners are advised to flush it down the toilet. By listing medicines that are potentially sought for misuse or abuse or medicines that can result in death from one single dose if inappropriately taken, the 'Flush List' is created for safety — rather than environmental sustainability — in mind. If the medication is not on the flush list, however, owners would throw them in trash following the steps for household disposal of medicines (**Fig. 1**), a practice again focusing on safety not environmental impact (FDA 2020a). In an effort to address the concern of environmental risk, FDA published a paper that evaluated the environmental and human health risks associated with the flushing of 15 active ingredients in medicines (Khan et al. 2017). The public health agency concluded that there were negligible risks with the flushing of those active ingredients, but acknowledged that additional data would be helpful for confirming the findings for some of the medicines (FDA 2020b). The FDA study, however, did not address the risks associated with the practice of disposing of unwanted pharmaceuticals in household trash. In fact, the latter scenario encompasses a far wider range of active pharmaceutical ingredients and presents a much more common practice for household disposal of unwanted pharmaceuticals. Prior to the pandemic, a cross-sectional two-phased study (n = 306) was conducted in Southern California, United States which showed that 'throwing medications in the trash' was the most common method for the disposal of medications among households (63%), and half of the surveyed households (50%) would throw those in trash during drug take-back events, followed by flushing down the toilet (26%) (Law et al. 2015). No significant relationship was found between age, ethnicity, education, income, insurance and the number of unused medications among the households. A recent study conducted by Health Products Stewardship Association showed that one in three Canadians do not know about proper disposal for unwanted medications, despite the fact that 90 percent of pharmacies offer take back programs within the participating provinces (HPSA 2021). Surveys in the Organisation for Economic Co-operation and Development (OECD) countries showed an average per capita spending of 564 USD per year on retail pharmaceuticals in 34 countries, and that 'throwing in waste bin' and 'flushing down the toilet or sink' represent the most common methods of disposal in households in 10 of 13 countries surveyed between 2009 and 2018 (**Fig. 2**). No survey data, however, have been published to date on the methods of disposal of expired or unwanted pharmaceuticals by the public under the impact of the COVID-19 pandemic.

As the world's most populous nation, China has established the second largest market for pharmaceutical products, with a global share of about 8% in sales in 2020 (Statista 2022b). In the "Expired Drugs Recycling in Chinese Families (2004-2014)", a white paper published in 2014 by a leading Chinese pharmaceutical manufacturer, it was reported that more than three quarters of households in China (78.6%) had medical cabinets in which 30% to 40% of medications in storage had expired over three years ago. Meanwhile, more than 80% of the households did not regularly clean up expired medications in their medical cabinets, which resulted in about 15,000 metric tons of expired drugs accumulated in households. An earlier survey conducted by the Shanghai Food and Drug Administration in 18 nationally representative regions across the country revealed that the principal method of disposal of unwanted pharmaceuticals in Chinese households was to throw them into the household trash, which accounted for 80.3% of the responses (SFDA 2009). In 2021, the Ministry of Ecology and Environment of China published the "National Inventory of Hazardous Wastes (2021)" with a "List of Exempted Hazardous Wastes" (MEEPRC 2021). As per the ministerial guidelines, unwanted pharmaceuticals and packaging materials in households are categorized as non-hazardous wastes, and only those collected as

'hazardous trash' under the new trash separation rules would be categorized as hazardous wastes. Although China introduced mandates on household trash separation in 2019, the new regulations are only applicable to municipalities and prefectural-level cities, where household pharmaceuticals and packaging materials are required to be disposed of as hazardous trash. Counties, towns, and rural areas are, however, exempted from these rules (GPRC 2021). To date, there is no national drug take-back program to collect expired or unwanted household pharmaceuticals in China.

Expired or unused medicines are potent bioactive substances that should be carefully managed to avoid potential toxicological effects in the environment (Michael et al 2019). Since the early 2000s, a significant amount of research efforts has been expended on understanding the occurrence and fate of pharmaceuticals and personal care products in the environment, as well as their effects on aquatic biota and human health through trophic transfer. Many pharmaceutical compounds show high persistence to the biological treatment processes in municipal wastewater treatment plants (Khasawneh and Palaniandy 2021). Researchers have reported the ubiquitous occurrence of pharmaceuticals and their metabolites in the natural environment. Residues of prescription and over-the-counter drugs were found in leachates of municipal solid waste landfills. Antibiotics that can alter natural bacterial species, along with anti-depressants, diabetes and hormone drugs were found in groundwater and surface water (Kümmerer 2009; Świacka 2022). Referred to ‘agents of subtle change’ by environmental scientists, pharmaceutical residues have high bioactivity and can cause various adverse effects in aquatic biota at low part-per-billion levels such as vitellogenin induction in male fish, gender and genital malformations in fish, and in some cases, the collapse of fish population. Furthermore, some studies showed that when exposed in laboratory settings, human cells could also be affected by these trace chemicals (Glassmeyer et al. 2009). Pharmaceutical residues in drinking water pose risks to the elderly, infants, and people who suffer from liver or kidney malfunction (Zarei et al. 2020; Mechelke et al. 2020).

The surging demand, stalled drug take-back programs, and a prolonging COVID-19 pandemic catalyzed the pressing need for a new imperative in managing the expired, unused, and other unwanted pharmaceuticals in households on a global scale. Unused, non-expiring drugs represent a vast resource to alleviate persisting shortages for some drugs and help other patients in need. Active pharmaceuticals ingredients have been reported to be extremely well preserved long after their labeled expiring dates. They present some of the most high-value chemicals and in the meantime, potent bioactive environment toxins once disposed of in the natural environment. In this article, we review current policies, challenges, infrastructure and technologies available for addressing this longstanding issue.

2. Disposal of drugs collected from various take-back programs

Drug take-back programs were established in European countries and other industrialized nations, including Australia and Canada, in the early 2000s, similar to those initiatives later implemented in the United States. The Article 127b of the European Union Directive 2004/27/EC (2004) of the European Parliament and of the Council requires that member States shall have appropriate collection systems in place for unused or expired medicinal products. A survey conducted by the European Federation of Pharmaceutical Industry Association reported that, three years later, 20 of the 28 nations surveyed established a pharmaceutical waste

collection scheme, most of which were pharmacy-based collection systems (Glassmeyer et al. 2009). In the United Kingdom, pharmacies are obliged to accept unwanted medicines from households and individuals (PSNC 2022), where waste contractors would collect those at regular intervals (NHS 2010). In Australia, the Return Unwanted Medicines (RUM) project is a national government-financed scheme for collecting expired and unwanted medicines from the general public via community pharmacies. Since the launch of the RUM project in December 2002, a total of 11,350 tons of medicines have been collected (NRDUM 2022). In Canada, natural health products—along with unused or expired prescription and over-the-counter drugs— can also be brought to local pharmacies (Government of Canada 2014), as a further effort to reduce the entry of consumer health care products in the environment. The Health Products Stewardship Association offer return programs for unwanted medications to reduce their likelihood of being thrown in the garbage, poured down the sinks, flushed or misused. Since its inception, the programs have collected nearly 3,800 tons of medications (HPSA 2022).

To date, the disposal of pharmaceuticals collected from consumer take-back programs has predominantly relied on incineration. In the United States, the EPA recommended incineration as the preferred method of disposal for household pharmaceuticals collected through take-back programs (EPA 2012). The DEA or other law enforcement agencies collecting controlled substances in these events are also obliged to dispose of these substances. Most controlled substances collected from take-back programs are incinerated. Within the European Union, the final disposal of unused and expired medication is generally done by high-temperature incineration (>1000 °C) equipped with adequate exhaust gas cleaning or alternatively, incineration at lower temperatures (850 °C or higher) in countries where municipal solid waste incineration is prevalent and owners are instructed to dispose of their unwanted medications in mixed household waste (OECD 2021). In Australia, returned medicines from the RUM project are disposed of by high-temperature incineration, in accordance with regulatory and EPA requirements (NRC 2006). Since the inception of the RUM project, more than 10,000 tons of unwanted or expired medicines collected from community pharmacies and wholesalers were incinerated in EPA-approved incinerators (RUM 2019).

In the lack of a 'pandemic protocol' for safe disposal of unwanted pharmaceuticals from individuals and households, the WHO guidelines perhaps offer the most appropriate point of reference for governments and authorities (**Table 3**). The WHO published these guidelines in 1999 to advise on the safe disposal of unusable pharmaceuticals from drug donations in emergencies and in countries where official assistance and advice are unavailable or insufficient. While incineration is universally effective in eliminating pharmaceutical wastes, it is among the most expensive and unsustainable methods of waste disposal and also requires access to specialized waste combustors to minimize the emission of toxic fumes from the incineration process (WHO 1999). Other methods of disposal, such as landfilling and waste encapsulation, do not have an impact on the activity of drugs. The active pharmaceutical ingredients retained in wastes would eventually leach out, promoting the growth of drug-resistance microbes in municipal solid waste landfills or polluting soils and groundwater through landfill leachates and leakages. Further, as these guidelines focus on the end disposal of donated pharmaceuticals, they did not address how unwanted pharmaceuticals could be collected, in a practical manner, from individual owners and households nationwide in a prolonged pandemic. In particular, the information gathering, logistics, and sorting present unprecedented challenges for environmental authorities to manage these pharmaceuticals ever since they became a recognized issue to environmental and public health agencies.

3. Waste minimization and recycling efforts

Minimization and recycling generally offer the most sustainable strategies for waste management, and pharmaceuticals are no exception. France and Japan offer valuable lessons on tackling the issue of unwanted pharmaceuticals in households. As one of the early countries tackling this issue, France founded the National Pharmaceutical Recycling Association in 1993 which, apart from the recycling of pharmaceutical packaging, recycles all unwanted medicines, including those within or beyond their expiration date. Recycling bins were placed at retail pharmacies where unwanted drugs were collected voluntarily and free of charge. Nearly 90 percent of pharmacies in France participated in this initiative. Nearly 11,000 tons of unused medicines were recovered across the country in 2016. In 2018, 80% of the French population reported returning their unused medicines to their pharmacists, and 60% did so on a routine basis. Once collected, the unwanted medicines were roughly separated into the 'reusable' and 'to-be-destroyed' batches. Pharmaceutical manufacturers or wholesalers would pick up those collected medicines from pharmacies and complete the fine-sorting. After quality checking, unopened and non-expiring medicines would be donated to domestic or international humanitarian organizations collaborating with the Association, which will then distribute these to individuals or countries in need of the medicines. Expired drugs containing usable ingredients would be sent to institutions or laboratories for extraction and reuse. Expired drugs and packaging that are deemed completely useless would be transported as medical wastes to specialized facilities for incineration. In Japan, there is a more innovative model for co-managing household pharmaceuticals where households are responsible for regularly cleaning out their expired drugs while pharmaceutical companies, which leave their medical cabinets in customers' homes for free, charge their customers only for the quantities of drugs they take and periodically take away the expired medicines and replenish the cabinets with new ones. The 'pay-as-you-go' model, which is common in Japanese households and similar to soda drinks kept in refrigerators in hotel rooms, minimizes the amounts of wastes of pharmaceuticals generated in households in the first place, which offers a valuable example for other countries.

In China, a pharmaceutical manufacturer initiated the "Expired Medicine Collection & Change-for-Free" program for households in 2004 (GPHL 2018a). Since its launch, over 1,500 tons of expired medications have been collected from individuals and households between 2004 and 2018. In 2018, a group of major pharmaceutical companies and logistics firms joined forces and set up the "National Coalition for Expired Medicine Recycle" (GPHL 2018b). The non-government-led initiative became the first and the only nationwide scheme for collecting expired medications from households. Since then, logistics and information technology have played an increasingly important role in such efforts. Under this new scheme, owners would scan a 20-digit barcode on the product package with their mobile apps, and then fill in their contact information to arrange pick-ups for their expired medications. The whole process can be done with a smart phone at home and is free of charge. The collected expired medications would then be shipped to centralized facilities and incinerated at 1200℃. This service, however, is only offered for a limited time every year between March 13–31, which is only available in seventeen metropolitan areas with high population densities and modernized logistics services in place.

In the United States, the re-distribution of unused, non-expiring drugs has long been advocated as a means of better serving patient's needs. The 2013 National Health Interview Survey, conducted by the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC) administering face-to-face

interviews in a nationally representative sample of households, found that about 8% of adults in the U.S. do not take medicines as prescribed because they could not afford the costs (LeWine 2015). As of November 2021, drug donating is allowed in 38 states, and there are regulations in place to oversee the donation and re-distribution process. More than half of the states where laws have been passed have established operating programs for drug re-distribution. For instance, states like Colorado and Florida accept unused drugs prescribed for cancer treatments, while Georgia and Iowa accept all prescription and over-the-counter drugs as long as they are in sealed packaging (Recovery Village, 2021). Beyond the government-led drug donation programs, individuals could also contact authorized organizations including, most notably, World Medical Relief, GoodPill.org, Volunteers in Medicine, and Memorial Sloan Kettering Cancer Center. Most organizations only accept unused drugs in original packages with unbroken seals. In 2020, the World Medical Relief received 803,178 pounds (364 tons) of donated medications from donors around the globe, with an estimated value of $2.3 million.

4. Recovery of active pharmaceutical ingredients

Waste pharmaceuticals have been largely overlooked as a vast source of valuable chemical compounds. A recent study reported that most of the active ingredients in commonly discarded medicines continue to be stable for many years after their expiration dates printed on product labels (Marić et al. 2021). Most pharmaceutical ingredients have very high purities, are costly to make, and belong to a group of high-value chemicals if recovered. Adding to these incentives, the formulations of most chemical drugs are not complex, with common additives present in the product. Compared with natural products, they represent much ‘cleaner’ matrices for extraction and selective recovery of target compounds. Overall, recovering active ingredients is economically attractive than synthesizing those ingredients from scratch owing to the simplicity of drug ingredients in many products and the inexpensive separation and purification technologies available (Pratama et al. 2020).

The most studied techniques for recovering active ingredients from pharmaceuticals matrices involve solvent extraction. **Table 4** presents the advantages and drawbacks of solvent-based extraction methods (Sharma et al. 2019). However, these operations have the common drawbacks associated with the use of volatile and toxic organic solvents. New separation technologies based on aqueous biphasic systems were also investigated in recent research and employed to separate active ingredients from pharmaceutical solids and further to fractionate recovered compounds (Marić et al. 2021). Recently, Pratama et al. (2020) demonstrated the proof of concept of drug recycling by recovering active ingredients from unused tablets and capsules. The recovery process comprised three stages, namely, solid-liquid extraction, filtration, and crystallization, with yields of 58.7 wt.%, 73.1 wt.%, and 67.6 wt.% for acetaminophen, tetracycline HCl, and ibuprofen, respectively (**Fig. 3**). Liquid chromatography analyses showed that the recovered ingredients were of high purity when compared with the standards. Other methods such as membrane separation or chromatographic separation often require high energy inputs and time-consuming steps (Basaiahgari and Gardas, 2021).

Absorptive polymers, many of which are of a generic nature and available as industrial-grade bulk materials, display remarkable binding affinity and specificity for pharmaceutical compounds, showing high capacities, uptake rates, and compound selectivity that are superior to conventional porous adsorbents for extractive

recovery of compounds (**Fig. 4** and **Fig. 5**) (Han et al. 2010, 2012a, 2013a). Driven by a hybrid mechanism of adsorption and solid-phase partitioning, the materials function as 'solid-phase extractants' for compounds dissolved in aqueous phase (**Fig. 6**). The process takes place spontaneously, requiring no energy input or specialized equipment, and are safer than liquid-liquid extraction processes using volatile and flammable organic solvents.

5. The imperative of managing unwanted pharmaceuticals during and after COVID-19

With global weekly new infections exceeding 20 million and reaching new peaks, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants are still circulating in our communities, making the eradication of COVID-19 a distant goal in the near future (He et al. 2021; Wang and Han 2022; WHO 2022). In this context, new policies, mandates, and advice are needed to respond to the changing circumstances and urgent needs to protect the environmental and public health both under the impact of the current pandemic and beyond (Chen et al. 2021b; Han et al. 2021; Han and He 2021a; Han and He 2021b; Han and Zhang 2020; Wang et al. 2020). In particular, the global outbreak and continuation of the COVID-19 pandemic have brought the need for collection, sorting, and reuse of unwanted pharmaceuticals to an unprecedented level. Here, we propose a new integrative policy and technology framework for the collection and recycling of expired, unused, and unwanted medicines from individuals and households (**Fig. 7**). In this framework, owners need to first separate their unwanted medications into opened and unopened products. Opened pharmaceutical products need to be deposited at or mailed to collection points, then sent to centralized plants for incineration. For the unopened medications, users could utilize the existing Internet and logistics infrastructure by filling in the drug information including its commercial name, expiring date, quantity, and manufacturer and submitting this information via the Internet. Using the present day's technology, the easiest way to do this is to scan the barcode on the product package to automatically fill in the information and then to ask for the owners' confirmation before submission. The system auto-generates free, coded mailing labels, which can be printed individually and attached on each product for shipment by leaving those in the curbside mailbox for collection. In-person pick-ups or other human contact should be avoided during the COVID-19 pandemic to reduce the risks of viral transmission (Dai et al. 2020; Sun et al. 2021). Once arrived at sorting facilities, packages are further categorized by automatic sorting facilities after reading the printed codes and retrieving the information from an internet-based database. Based on the information submitted by owners, products are categorized by their active ingredients, expiration dates, and forms (e.g., pills, capsules, powders, gels). Unopened, non-expiring pharmaceuticals that are in shortages of supply are preserved for further quality check and potential re-distribution to patients in need. Other pharmaceuticals are sorted and prepared before being sent to specialized processing plants for subsequent extraction, recovery, and purification of their active ingredients into various products such as chemical reagents, veterinary drugs, or agrochemicals. Products with proprietary formulations are sent back to their manufacturers in bulk quantities for de-formulation and reuse. After processing, quality checks are implemented to ensure the purity and safety of products for their prospective use.

6. Conclusion

The increasing demand and use of pharmaceuticals have resulted in the accumulation of expired and unwanted pharmaceuticals in households, which may have reached unprecedented quantities in the COVID-19 pandemic. Inappropriate disposal of pharmaceuticals, an inevitable compromise due to lockdowns and resource shortage under the impact of the pandemic, poses a significant threat to the ecological system and public health. We reviewed the gaps in the current policies for the collection and disposal of household pharmaceuticals, and proposed a simple policy and technology framework for effective and sustainable management of unwanted pharmaceuticals in households in an epidemic or pandemic context. The integrated framework involves efforts from government agencies, drug manufacturers and other participating parties from the private sector, and more importantly, drug owners. Building on existing internet and logistics infrastructure, it enables owners to complete drug sorting and information gathering at the point of use, and generates labels with machine-readable codes to streamline the fine-sorting of unopened pharmaceuticals for subsequent processing or re-distribution. These will reduce the ongoing discharge of pharmaceutical compounds into the environment while recycle intact pharmaceutical products or raw chemical ingredients, thus closing the gap in current policies and practices of managing household pharmaceuticals. By circumventing the long-recognized difficulties in collecting and sorting household pharmaceuticals, this strategy may offer a feasible and timely solution to address the pressing issue of mounting unwanted pharmaceuticals while tap into the vast resource left in households around the globe.

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Fig. 1 Infographic on the disposal of "Non-Flush List" medicines in household trash. Adapted from Food & Drug Administration (FDA 2018). To reduce the risk of environmental contamination by active drug ingredients, some companies offer activated carbon-loaded pouches as an upgraded option to 'deactivate' drugs for safer disposal of medications at home, although data are lacking on their long-term performance (>28 days) or in the real environment (Deterra 2022; Herwadkar et al 2016; Gao et al. 2018). **Table 2 s**hows a compiled list of manufacturer's descriptions for seven products marketed to consumers for home disposal of medicines.

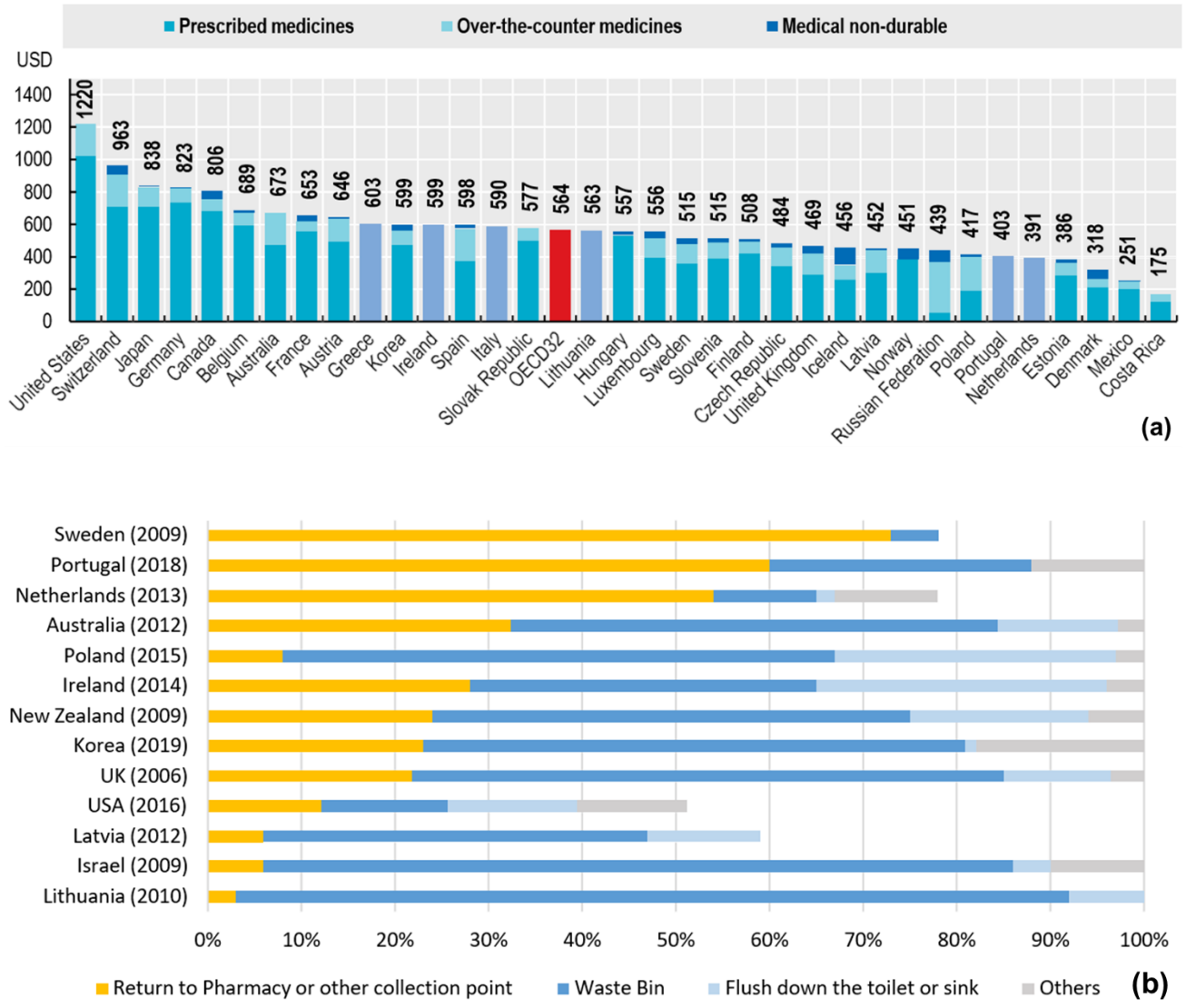


Fig. 2 (a) Expenditure on retail pharmaceuticals per capita, in 2017 or the nearest year, across Organisation for Economic Co-operation and Development (OECD) countries and adjusted for purchasing power. In the lack of national survey data on unwanted pharmaceuticals in households, expenditure data provide a rough indication for the amount of drugs in circulation and the amount of unwanted drugs generated in households **(b)** Household disposal practices of unused or expired medicines in selected OECD countries. Adapted from OECD (2021).

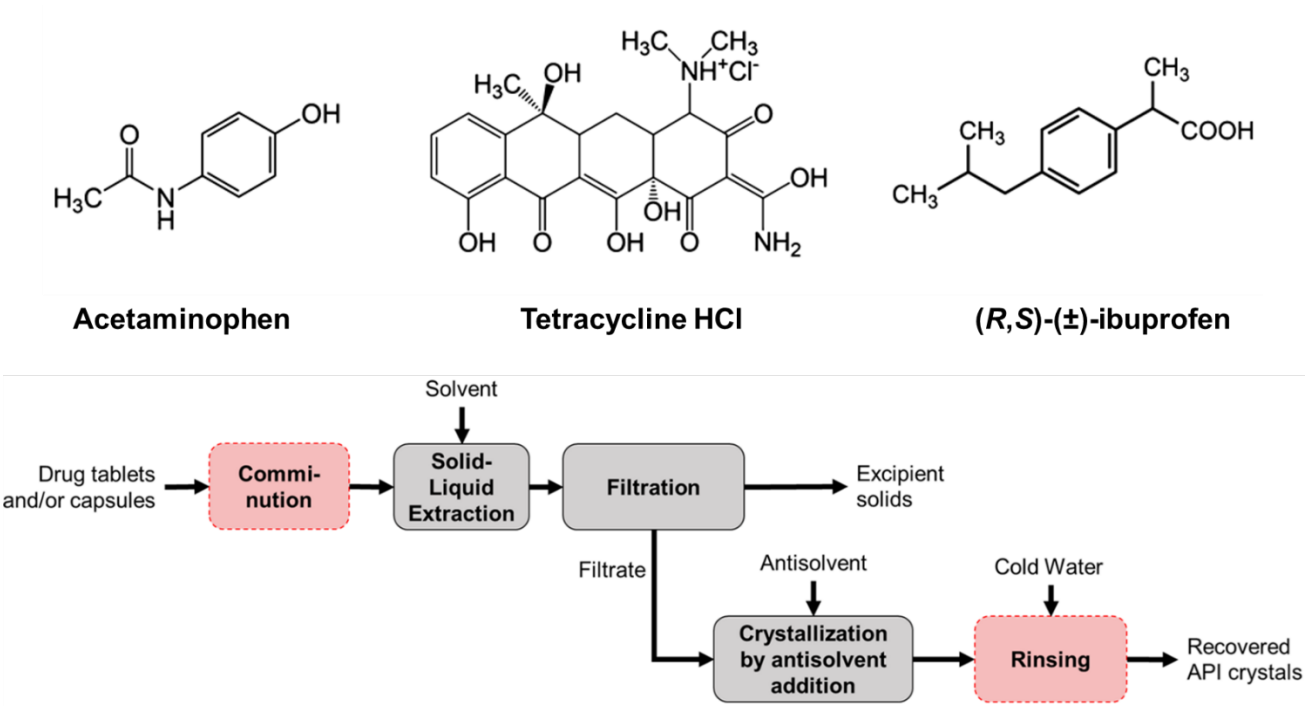


Fig. 3 Recovery of three active pharmaceutical ingredients from solid dosage form drugs. Gray shade denotes core operations. Red shade denotes optional operations. Adapted from Pratama et al. (2020).

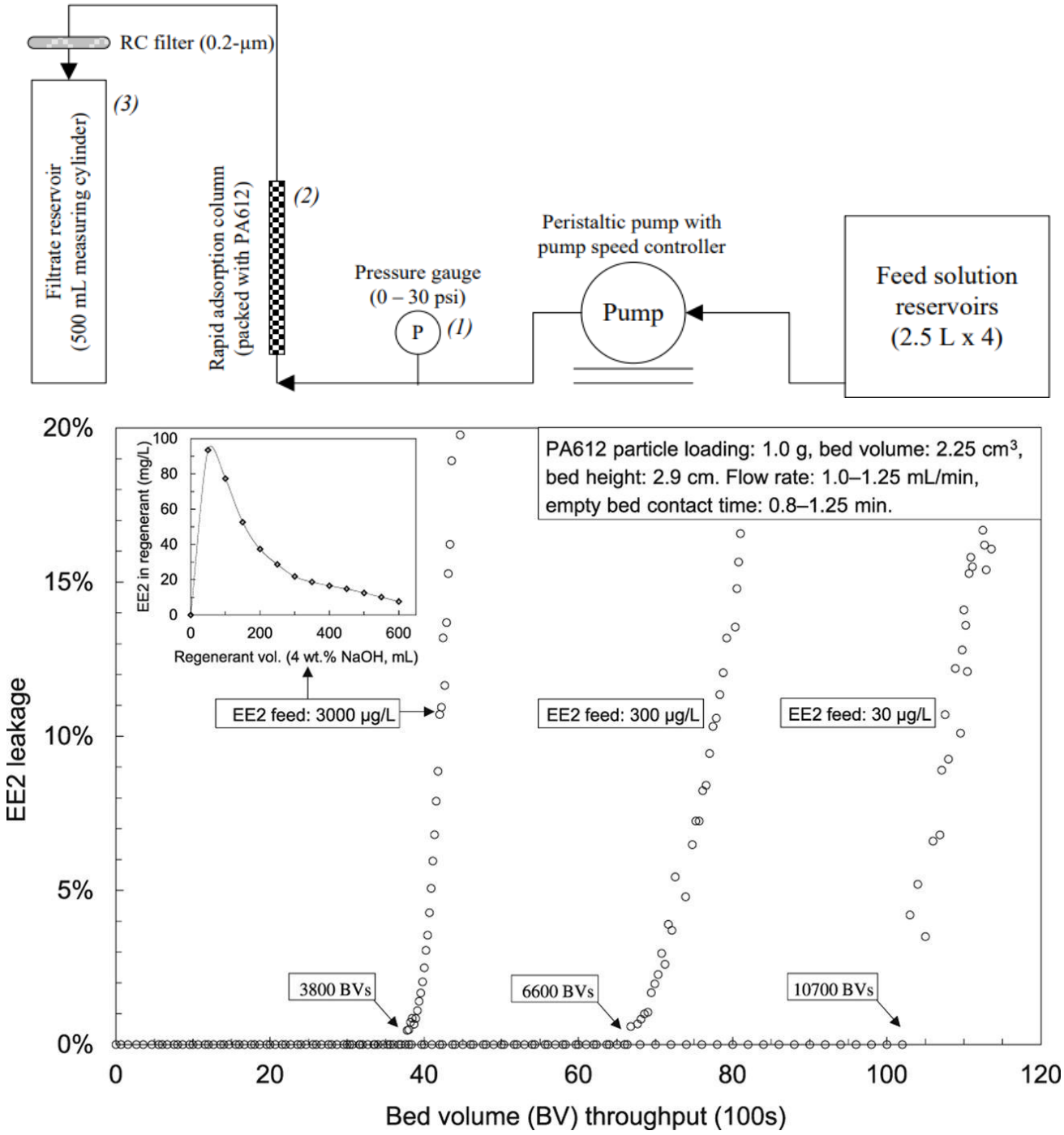
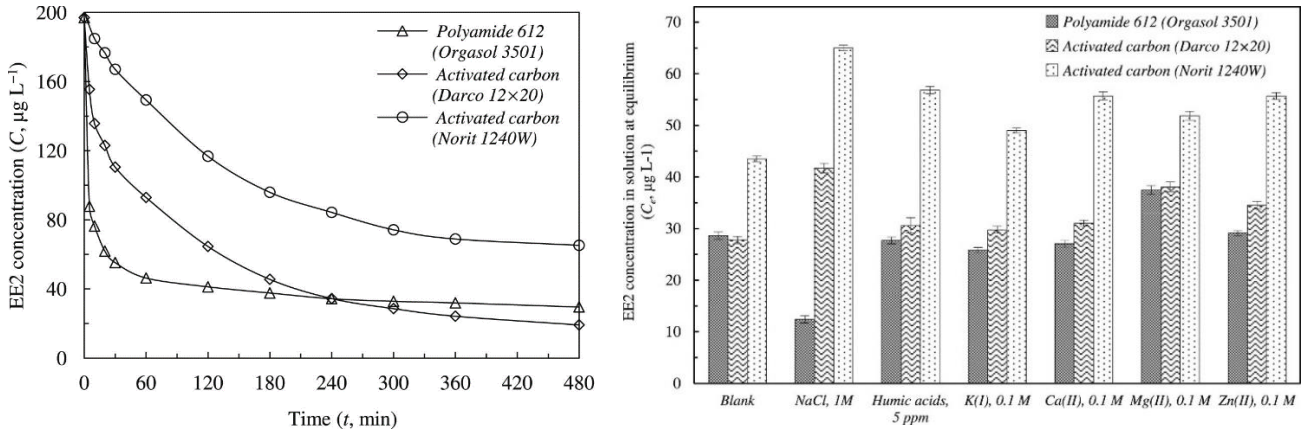


Fig. 4 (Top) a schematic diagram of the rapid column uptake apparatus for continuous capture of ethinylestradiol (EE2, CAS No. 57-63-6), a common active ingredient in birth control pills, from aqueous solutions. The column has a fixed end with an adjustable end made of Teflon to minimize solute adsorption. Filtrate was collected in a 500-mL measuring cylinder for real-time reading of filtrate volume. A pressure gauge was installed at the pump discharge to monitor the system pressure to detect blockage and leakage. When operating, the system pressure fluctuated at 10–15 psi (69–103 kPa). (Bottom) rapid column retention of EE2 by polyamide 612 particles. Feed concentrations (EE2): 30–3000 μg L^{-1} (*ca.* 0.1–10 μM); column loading: 1.0 g; bed volume (BV): 2.25 cm^3; bed height: 29 mm; flow rate: 1.0–1.25 BV min^{-1}; at 25 °C. Column breakthrough was determined by liquid chromatography of samples collected at regular intervals. Reprinted with permission of Elsevier B.V. from Han et al. (2012b).



(a) (b)

Fig. 5 (a) Uptake of ethinylestradiol (EE2, CAS No. 57-63-6), a common active ingredient in birth control pills, by polyamide 612 versus industrial-grade activated carbon adsorbents. **(b)** Effects of water chemistry on the uptake of EE2 on polyamide 612 versus activated carbon adsorbents. Conditions: initial concentration (EE2): 200 μg L^{-1}, dose of material: 0.2 g L^{-1}, at 25 °C. Error bars represent standard deviations from triplicates. Adapted with permission of Elsevier B.V. from Han et al. (2013b).

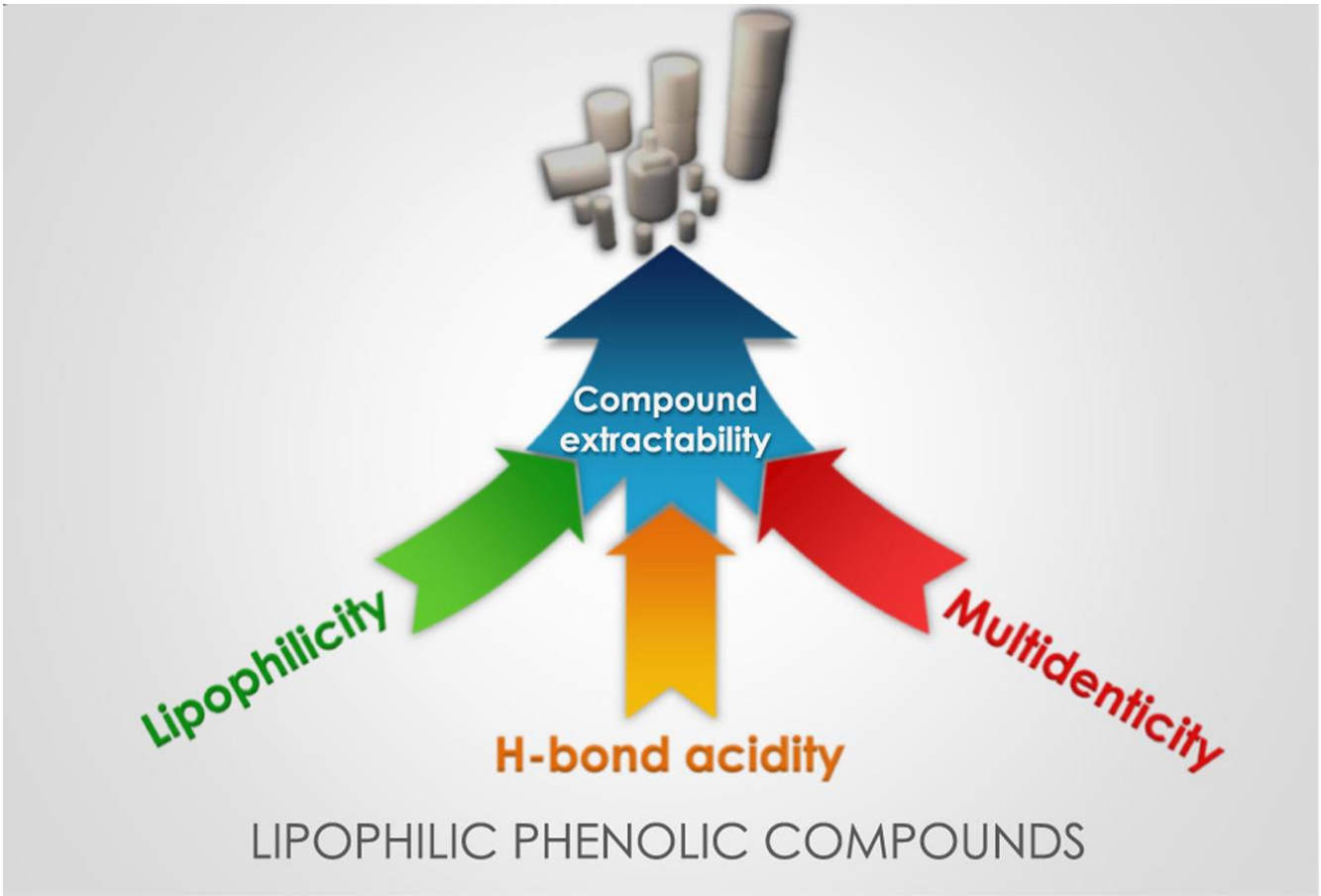


Fig. 6 Flexible ether-type polyurethane foam, a consumer-grade polymer material, is a promising absorptive polymer used for the extractive recovery of neutral, moderately hydrophobic compounds with phenolic and other electrophilic moieties, offering high uptake capacities, compound specificity, and ease of regeneration. Reprinted with permission of Elsevier B.V. from Han et al. (2017).

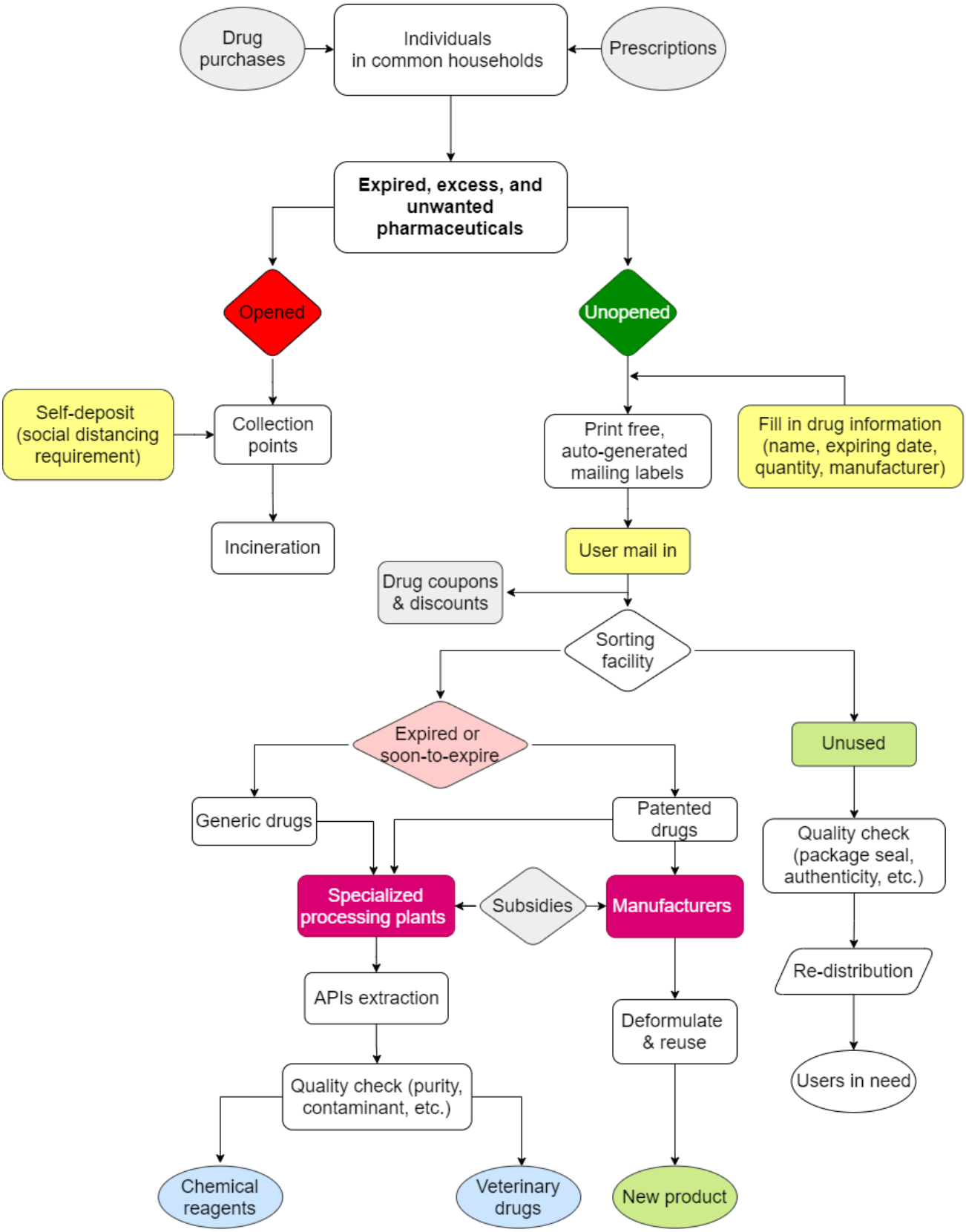


Fig. 7 A proposed integrated policy and technology framework for managing expired, unused, and unwanted pharmaceuticals in households, an unintended legacy of the novel coronavirus disease (COVID-19) pandemic and beyond

Table 1. Examples of products on the 'Flush List' for certain medicines recommended by U.S. Food and Drug Administration, adapted from FDA (2020b)

Drug Name	Examples of Products on the Flush List
Drugs That Contain Opioids	
Any drug that contains the word "buprenorphine"	BELBUCA, BUAVAIL, BUTRANS, SUBOXONE, SUBUTEX, ZUBSOLV
Any drug that contains the word "fentanyl"	ABSTRAL, ACTIQ, DURAGESIC, FENTORA,ONSOLIS
Any drug that contains the word "hydromorphone"	EXALGO
Any drug that contains the word "meperidine"	DEMEROL
Any drug that contains the word "morphine"	ARYMO ER, AVINZA, EMBEDA, KADIAN, MORPHABOND ER, MS CONTIN, ORAMORPH SR
Drugs That Do Not Contain Opioids	
Any drug that contains the term "sodium oxybate" or "sodium oxybates"	XYREM, XYWAV
Methylphenidate transdermal system	DAYTRANA

Notes: Owners are referred to specific disposal instructions in each medicine's labeling. The most current drug labeling can be found at http://www.fda.gov/drugsatfda or https://nctr-crs.fda.gov/fdalabel/ui/search. A peer-reviewed study was published by the U.S. Food and Drug Administration in 2017, addressing the environmental and human health risks of 15 active ingredients found in the 'Flush List' medicines (Khan et al. 2017).

Table 2. Manufacturer's descriptions for seven products marketed to consumers for home disposal of medicines, adapted from CEHS (2017).

Product name[a]	**Active ingredient**	**Mode of Action**	**Final disposal instructions**	**List price**[b]
Deterra (MedsAway)	Activated carbon	Adsorption of chemicals to carbon	Garbage / solid waste system	\$4.99: single pouch / 15 pills \$6.99: large pouch / 90 pills \$34.99: 1.8 L bottle / 450pils
DiposeRx.	Cross-linking polymer	Unknown (ingredients not identified)	Garbage / solid waste system	Not stated
Drug Buster	Activated carbon	Adsorption of chemicals to carbon	Garbage / solid waste system per local regulations	\$9.95: 4 oz / 50 pills \$15.99: 16 oz / 300 pills \$34.99: 64 oz /1500 pills
Element MDS	Organic plant-based powder	Unknown (ingredients not identified)	Garbage / solid waste system	\$6.99: 17 oz / 500 pills not sold individually. \$349.50 for 50 kits
Pill Catcher	Bentonite clay	Adsorption of chemicals to clay	Garbage / solid waste system	\$4.95: pint / 120 pills \$6.96: quart / 300 pills \$22.60: gallon /1500 pills
Pill Terminator	Calcium hypochlorite, Fuller's earth, absorbent polymer	Oxidation and adsorption	Garbage / solid waste system	\$9.95: 300 mL / 300 pills 524.95: gallon size / capacity not stated
Rx Destroyer	activated carbon and proprietary agents	Adsorption of chemicals to carbon	Garbage / solid waste system. Check federal, state, local regulations	\$4.16: 4 oz / 50 pills \$8.75: 16 oz / 300 pills \$48.75: 1.0 gallon / 3000 pills Sold in cases

Notes: (a) Deterra (when used by healthcare facilities), Drug Buster, and Rx Destroyer are for use with non-hazardous pharmaceuticals only, as specified by manufacturers. **(b)** List prices were of March 2017 (in US dollars). Further information on these products is compiled in the report for San Francisco Department of the Environment (CEHS 2017).

Table 3. Guidelines on disposal of unwanted pharmaceuticals from drug donations in and after emergencies by the World Health Organization, adapted from WHO (1999)

Disposal methods	**Types of pharmaceutical**	**Comments**
Return to donor or manufacturer, transfrontier transfer for disposal	All bulk waste pharmaceuticals, particularly antineoplastics.	Usually not practical - transfrontier procedures may be time consuming
High temperature incineration with temperatures greatly in excess of 1200°C	Solids, semisolids, powders, antineoplastics, controlled substances.	Expensive
Medium temperature incineration with two-chamber incinerator with minimum temperature of 850°C. Cement kiln incineration	In the absence of high temperature incinerators, solids, semi-solids, powders. Controlled substances.	Antineoplastics best incinerated at high temperature
Immobilization		
Waste encapsulation	Solids, semi-solids, powders, liquids, antineoplastics, controlled substances.	
Inertization	Solids, semi-solids, powders, antineoplastics, controlled substances.	
Landfill		
Highly engineered sanitary landfill	Limited quantities of untreated solids, semi-solids and powders. Disposal of waste pharmaceuticals after immobilization preferable. PVC plastics.	
Engineered landfill	Waste solids, semi-solids and powders, preferably after immobilization. PVC plastics.	
Open uncontrolled non-engineered dump	As last resort untreated solids, semisolids, powders - must be covered immediately with municipal waste. Immobilization of solids, semi-solids, powders **is** preferable.	Not for untreated controlled substances
Sewer	Diluted liquids, syrups, intravenous fluids, small quantities of diluted disinfectants (supervised)	Antineoplastics, and undiluted disinfectants and antiseptics not recommended
Fast-flowing watercourse	Diluted liquids, syrups, intravenous fluids; small quantities of diluted disinfectants (supervised)	Antineoplastics, and undiluted disinfectants and antiseptics not recommended
Burning in open containers	As last resort, packaging, paper, cardboard	Not acceptable for PVC plastics or pharmaceuticals
Chemical decomposition	Not recommended unless special chemical expertise and materials available	Not practical for quantities over 50 kg

Table 4. Solvent-based extraction techniques for recovery of active pharmaceutical ingredients from expired or unused medications, adapted from Sharma et al. (2019)

	Ultrasound-assisted extraction	**Microwave-assisted extraction**	**Supercritical fluid extraction**	**Accelerated solvent extraction**
Brief description	Sample is immersed in solvent and submitted to ultrasound using a ultrasonic probe or bath	Sample is immersed in solvent and submitted to microwave energy	Sample is placed in a high-pressure vessel and crossed continuously by the supercritical fluid	Sample is heated by a conventional oven and crossed by the extraction solvent under pressure
Extraction time	10–60 min	3–30 min	10–60 min	10–20 min
Sample size	1–30 g	1–10 g	1–5 g	1–30 g
Solvent use	50–200 ml	10–40ml	2–5 ml (solid trap); 30–60 ml (liquid trap)	15–60 ml
Investment	Low	Moderate	High	High
Advantages	Easy to use	Rapid Easy to handle Moderate solvent consumption	Rapid Low solvent consumption Concentration of the extract No filtration necessary Possible high selectivity	Rapid No filtration necessary Low solvent consumption
Drawbacks	Large amount of solvent consumption Filtration step required	Extraction solvent must absorb microwave energy Filtration step required	Many parameters to optimize	Possible degradation of thermolabile analytes