"Optimizing Medication Management: A Technological Ecosystem for Advanced Pharmaceutical Packaging to Enhance Remedies and Minimize Medicinal Waste"

H M Manjula, Sree keerthana G, S A Asim Ahmed, Ankitha Darapaneni, Tharak Chandra, Mudassir Ahmed

Computer science engineering (DATA SCIENCE) 5th President University 5th Itgalpur Rajanakunte, Yelahanka, Bangalore, Karnataka, 560064 India

Abstract: With the advancement of science and technology, the pharmaceutical industries have flourished drastically in recent years. However, the domain of pharmaceutical waste management is not in check and hence the improper disposal of pharmaceutical waste like dumping, burning, flushing, land filling has led to harmful impact in the environment like air and water pollution, change in aquatic ecosystem, destruction of flora and fauna, genetic changes, antimicrobial resistance, etc. The idea of reusing dispensed medicines is appealing to the general public provided its benefits are illustrated, its risks minimized, and the logistics resolved. For example, medicine reuse could help reduce medicinal waste, protect the environment and improve public health. A literature survey is undertaken to lay down the groundwork for implementing technologies on and around pharmaceutical packaging in order to meet stakeholders’ previously expressed misgivings about medicine reuse (‘stakeholder requirements’), and propose a novel ecosystem for, in effect, reusing returned medicines.

Methods: A structured literature search examining the application of existing technologies on pharmaceutical packaging to enable medicine reuse was conducted and presented as a narrative review.

Results: Reviewed technologies are classified according to different stakeholders’ requirements, and a novel ecosystem from a technology perspective is suggested as a solution to reusing medicines.

Conclusion: Active sensing technologies applying to pharmaceutical packaging using printed electronics enlist medicines to be part of the Internet of Things network. Validating the quality and safety of returned medicines through this network seems to be the most effective way for reusing medicines and the correct application of technologies may be the key enabler.

Keywords: Reuse of medicines; reduce medicinal waste; intelligent pharmaceutical packaging; medicine re-dispensing; theory of planned behavior.
1. Introduction

Medicinal waste has not only been a problem in the NHS (National Health Service) [1], but also a challenge in other countries in terms of public health, the environment and governmental expenditures [2,3,4]. Trueman et al. [5] reported that £300M of prescribed medicines are wasted every year mainly through medication non-adherence. Together with those unused, unwanted and unexpired medicines, they are major sources of preventable medicinal waste that can currently only be disposed of through managed (e.g., disposal centers at community pharmacies) and unmanaged methods (e.g., domestic sewage, public bins, etc.). One of the ways to tackle medicinal waste is to explore the idea of medicine reuse, which is currently not permitted in the UK [6,7]. A legally approved re-dispensing of medicines scheme has started to work in some areas of the world such as the SIRUM (Supporting Initiatives to Redistribute Unused Medicine (https://www.sirum.org/)) originating from the California [8], the Pharmaceutical donation and reuse programs operating now in many states of the US [9], and the GivMed (https://givmed.org/en/) programme facilitating access to leftover medicines using a smartphone app in Greece [7]. However, there are restrictions to the types and the sources of medicines to be reused since the quality and safety of the returned medicines are not guaranteed [10].

Donating medicines to remote areas that lack resources is another way of reducing medicinal waste through recycling medicines. Nevertheless, the reusing of dispensed medicines is generally not allowed because a proper way of validating the quality of returned medicines is not yet available. Thus, prescribed medicines from individuals are usually not allowed to be donated abroad either [11,12]. A sustainable pharmaceutical supply chain (PSC) management may provide an alternative solution to reducing medicinal waste through the concept of reverse flows. Viegas et al. [13] classifies reverse flows into donation, Reverse Logistics (RL) and Circular Economy (CE), where CE illustrates a close loop supply chain paving the way to reuse returned medicines. The complicated communication flows between a large numbers of PSC stakeholders could be an obstacle blocking a smooth reverse flow implementation. Pharma 4.0, an extension of Industry 4.0 to pharmaceutical manufacturing, may help establish seamless connections between stakeholders through Internet of Things (IoT) technologies [14,15]; however, the big concern in managing and monitoring the quality of returned medicines still needs to be resolved.

The World Health Organization (WHO) defines pharmaceutical waste as undesirable pharmaceuticals, including expired, unused, spilled, and infected pharmaceutical products, medications, vaccines, and sera that are not required and should be disposed of appropriately [16]. The volume of pharmaceutical waste has increased primarily due to growth in the number of patients and prescriptions and the use and overproduction of medicines. The increase in unused, expired, and misplaced medicines contributes to medicine shortages, higher percentages of pharmaceuticals waste, and increased medicine disposal costs, and it is a growing concern globally requiring a systemic approach to its resolution [17].

The last phase of the pharmaceutical waste is disposal, traditional burning or non-burning technique utilized. It is essential to note that, out of all pharmaceutical waste, only 15% is hazardous, whilst the remaining 85% is general [18]. Large amounts of prescribed pharmaceutical waste are found in the waterways, streams and groundwater, and it has similarly been shown that a percentage of these are affecting the water and the climate [19]. The WHO classification of different types of healthcare waste is [20]:

- Pathological; this includes body parts, body fluids, human waste, and tissue waste and animal corpses that are contaminated;
- Pharmaceutical; this is either unused, contaminated medicine or medicine which has expired;
- cytotoxic; genotoxic waste (highly hazardous);
  - sharps; includes syringes, needles, and blades, etc.;
  - Infectious; this usually contains blood or any bodily fluid which is contaminated and could, therefore, infect other people when they come into contact;
- Non-hazardous; these waste materials can not cause any chemical, radioactive, biological, or physical dangers; and,
• Radioactive; products that are infected by radionuclides.

These different types of waste require differing methods of disposal and/or new approaches in order to reduce or eliminate waste. It is important to determine the most suitable method to help preventing/reducing the negative consequences of the disposing methods on the environment, specifically on water, soil, air, and on human well-being [17,18].

The circular economy (CE) is a holistic philosophy that is conveyed through a system for managing and preserving resources ‘in use as long as possible through recovery and reuse’, hence circularity [21]. The CE approach closes the gap between production and the life cycle of the natural ecosystem upon which individuals rely for business and physical survival. It signposts practical ways of eliminating waste, transforming biodegradable and non-biodegradable waste, and promoting reuse and recycling. In CE, a distinction is made amongst different choices of circularity, represented as the R-model of 3R, 4R, or even 9R models (the 9R model being the optimal application of CE incorporating Refuse, Rethink, Reduce, Reuse, Repair, Refurbish, Remanufacture, Repurpose, Recycle, and Recover) [22,23]. Kirchherr et al. [24] claimed that the CE is “the combination of reduce, reuse and recycle activities” to ensure systematic change. The CE has been rapidly growing to realise the United Nation Sustainable Development Goals (SDGs) and as an alternative strategy for business advancement. In the CE, products and services operate in closed loops (being produced and then recycled for further use) and they are intended to work in harmony with the environment. The Ellen MacArthur Foundation, which was founded in 2010 and aims to accelerate progress towards a regenerative CE [25], defines the CE as a move from a linear model of resource consumption, which pursues a take-make-dispose design, to an economy that is restorative by intention. The CE associates the supply and demand of supply chain industries in order to increase resource efficiency and help achieve sustainable production and consumption [24].

Sufficiency economy philosophy (SEP) is another approach that has been considered in academic circles as contributing to the sustainability agenda. SEP is defined by the United Nations [26] as “an innovative method for development that is designed for practical application over a wide range of problems and situations”. The objective of SEP is to improve planning procedures in order to ensure sustainability, manage changes in the world and utilize natural resources in a capable way while preserving nature.

effective consumption of resources; reasonableness, which concerns objectively choosing the degree of products adequacy while considering the elements that are involved and the normally expected results; and, risk management, which entails adapting that is based on reasonable effects and changes that are projected by considering the likelihood of future circumstances from different viewpoints [25].

The aim of this study was to determine whether the application of CE principles reduce pharmaceutical waste and support sustainability in the Pharmaceutical Supply Chain (PSC). The rationale of the aim of this research was to identify ways to decrease the negative environmental impact, costs and promote sustainable supply chain and eco-design through the application of CE principles in the PSC. By identifying how the CE principles and the R-strategies can be used in the pharmaceutical supply chain it will be possible to determine how the negative impact of pharmaceutical waste be reduced in terms of costs, sustainability, and increasing circularity. To achieve this aim, the following objectives were posited: (1) to ascertain how pharmaceuticals waste is created, (2) to better understand how this waste is managed, (3) to outline how it is safely disposed, and (4) to determine how pharmaceuticals waste can be reduced and better managed through the adoption of CE principles.

2. Materials and Methods

A review of current pharmaceutical waste management studies was undertaken to document how pharmaceuticals be reused and whether implementation of the CE philosophy and associated principles could help to reduce waste. The following keywords were used for the primary search: ‘Medicines’ AND ‘Pharmaceutical’ AND ‘Pharmaceutical Waste’ OR ‘Drugs’ OR ‘Pharmaceutical Return’ OR ‘Disposal’ OR ‘Hospitals’ OR ‘Pharmaceutical Supply Chain’ OR ‘Medicines Reuse’ OR ‘Circular Economy’ OR ‘Circular Economy Principles’.

First, the titles and abstracts of each article were screened, and the most significant articles were selected. Second, the related abstracts were chosen, and the full form of each selected article was retrieved. A few papers were eliminated after their selection, as described below. Journals and papers published in English were chosen. Articles, papers, and studies published before July 2020 were explored while using Elsevier, Google Scholar, MDPI, PubMed, SAGE, and Science Direct.
To be included in the review, articles/papers had to be related to pharmaceuticals, medicine reuse, waste management, and/or CE, and they had to present new and/or relevant information. Articles/papers on approaches to waste management improvement, legislation, the PSC, waste generation minimization, and CE application were also included. Excluded papers are not explicitly related to the keywords highlighted above.

The search was conducted while using electronic databases, avoiding manual exploration. Duplications were eliminated. Non-academic grey literature was also searched in Google utilizing similar keywords. These sources included journalistic articles, reports, and WebPages on pharmaceuticals waste and CE. A conventional quality examination was not utilized, as one of the goals of this study was to gather a broad base of proof, including all of the procedures and studies related to gathering in-depth literature data. Figure 1 shows the areas of the literature that were reviewed to meet the aim of this study.

3. Design Procedure

Designing a new medicine is a complex and highly regulated process that involves multiple stages of research, development, testing, and regulatory approval. Reusing the medicine design procedure generally implies leveraging existing knowledge, processes, and data to streamline the development of new drugs. Here is a simplified overview of the typical steps involved in the medicine design procedure:

1. Literature Review and Data Mining:
   - Conduct a comprehensive review of scientific literature and databases to identify existing drugs with potential therapeutic effects on different diseases.
   - Utilize data mining and bioinformatics tools to analyze large datasets, including genomic, proteomic, and clinical data, to identify potential drug candidates.

2. Target Identification and Validation:
   - Identify new disease targets or validate existing targets associated with the repurposing candidate.
   - Consider both on-label and off-label uses for the drug.

3. Biological and Mechanistic Studies:
   - Conduct in vitro studies to understand the biological mechanisms by which the drug interacts with the target.
   - Investigate the pharmacological effects and potential side effects of the drug.

4. Preclinical Studies:
   - Perform preclinical studies to evaluate the safety, pharmacokinetics, and efficacy of the repurposed drug in relevant animal models.
   - Assess the potential dosage and formulation needed for the new therapeutic indication.

5. Clinical Trial Design:
   - Design well-controlled clinical trials to test the safety and efficacy of the repurposed drug in the target patient population.
   - Consider adaptive trial designs to optimize efficiency and flexibility.

6. Regulatory Planning:
   - Consult with regulatory agencies early in the process to understand their requirements for repurposed drugs.
   - Develop a regulatory strategy that considers existing safety data and the potential for expedited approval pathways.
7. Clinical Trials (Phase I, II, III):
   - Conduct Phase I trials to assess safety, pharmacokinetics, and dosage in a small group of patients.
   - Progress to Phase II trials to evaluate efficacy and optimal dosage in a larger patient population.
   - Conduct Phase III trials to confirm the drug's effectiveness and monitor long-term safety in a larger and more diverse patient group.

8. New Drug Application (NDA):
   - Compile and submit a new drug application to regulatory agencies, including comprehensive data from preclinical and clinical studies.
   - Highlight the existing safety profile of the drug, which may facilitate regulatory approval.

9. Post-Marketing Surveillance:
   - Implement post-marketing surveillance to monitor the drug's safety and efficacy in a real-world setting.
   - Continuously assess and update the drug's risk-benefit profile.

10. Market Access and Commercialization:
    - Develop a market access strategy to ensure the repurposed drug reaches the intended patient population.
    - Establish partnerships with stakeholders, including healthcare providers and payers.

Throughout the process, collaboration with academic institutions, pharmaceutical companies, and regulatory bodies is crucial. Additionally, ethical considerations, patient safety, and regulatory compliance should always guide the reuse of medicines. It’s important to note that not all repurposing attempts may be successful, and careful evaluation and validation are essential at each stage of the process.

4. Results

4.1. Pharmaceutical Waste Management

The literature review identified three clearly defined areas of focus when examining pharmaceutical waste management. These are discussed individually below.

4.1.1. Waste Creation

Instances of pharmaceuticals waste may be caused by patients who are unable to utilize all of their administered pharmaceuticals due to unfavorable impacts (side effects), daily dosage modifications, health improvements, and the expiry of medicines, doctors’ prescribing practices, or dispensers’ practices. Non-adherence to prescriptions can also cause stockpiling of leftover medications in the home. According to the WHO, half of the patients neglect to take medication effectively [26]. As such, families and patients around the world are in possession of unused or terminated prescriptions, and the associated dangers have prompted research interest. Many individuals who stockpile undesirable, unused, or expired pharmaceuticals in their homes dispose of them through waste containers or sinks or by flushing them down the toilet. It is important to realize that discarding unused or terminated pharmaceuticals through non-permitted methods affects the environment and individual wellbeing [6,27].

User Remedy for Medicine Algorithm:

Creating an algorithm for user reuse of medicine involves developing a system that considers various factors to suggest or guide users in repurposing existing medications. Here's a basic outline of such an algorithm:

1. User Input:
   - Gather information about the user, including medical history, current medications, and any existing health conditions.

2. Disease or Condition Identification:
   - Identify the specific disease or condition for which the user is seeking medication reuse.

3. Drug Repurposing Database Search:
   - Utilize a drug repurposing database or knowledge base that contains information on existing drugs and their potential uses for different conditions.
   - Implement algorithms to match the user's condition with potential repurposed medications.

4. Risk Assessment:
   - Evaluate the safety and potential risks of repurposing a particular medication for the identified condition.
   - Consider known side effects, contraindications, and the user's individual health profile.

5. Effectiveness Assessment:
   - Assess the efficacy of the repurposed medication for the user's specific condition.
   - Consider available clinical evidence, studies, and real-world data.
6. Dosage Adjustment:
   - Calculate and recommend appropriate dosage adjustments based on the repurposed use of the medication.

7. Interaction Analysis:
   - Evaluate potential drug interactions with the user's existing medications.
   - Consider the overall impact on the user's health and well-being.

8. Monitoring Plan:
   - Develop a monitoring plan for the user, including recommended follow-up visits, laboratory tests, or other assessments to track the effectiveness and safety of the repurposed medication.

9. Educational Resources:
   - Provide educational resources to the user, explaining the rationale behind the repurposing recommendation, potential benefits, and risks.
   - Ensure the user is informed and understands the decision-making process.

10. Feedback and Iteration:
    - Allow users to provide feedback on their experience with the repurposed medication.
    - Implement mechanisms to continuously improve the algorithm based on user feedback and emerging clinical evidence.

11. Privacy and Security Measures:
    - Implement robust privacy and security measures to protect the user's health information.

12. Integration with Healthcare Providers:
    - Facilitate communication and information exchange with healthcare providers, ensuring that the user's decision to repurpose medication is coordinated with their overall healthcare plan.

Admin Remedy for Medicine Algorithm:

Creating an algorithm for administering remedies or medications involves considering various factors related to patient health, medical history, and specific treatment requirements. Here's a generalized outline for an algorithm that an administrator or healthcare provider might follow:

1. Patient Assessment:
   - Gather patient information, including medical history, current medications, allergies, and any existing health conditions.
   - Consider the patient's age, weight, and other relevant demographic factors.

2. Diagnosis or Condition Identification:
   - Identify the specific diagnosis or health condition for which the remedy or medication is needed.

3. Clinical Guidelines and Protocols:
   - Refer to established clinical guidelines and protocols for the treatment of the identified condition.
   - Ensure adherence to evidence-based medicine and best practices.

4. Medication Selection:
   - Choose the appropriate medication based on the diagnosis, considering factors such as efficacy, safety, and patient-specific characteristics.
   - Consider potential drug interactions and contraindications.

5. Dosage Calculation:
   - Calculate the correct dosage based on the patient's weight, age, renal function, and other relevant factors.
   - Consider any adjustments needed for special populations (e.g., pediatric or geriatric patients).

6. Administration Route:
   - Determine the most suitable route of administration (oral, intravenous, intramuscular, etc.) based on the medication and patient's condition.

7. Patient Monitoring:
   - Establish a monitoring plan to track the patient's response to the medication.
   - Define parameters for assessing effectiveness and potential side effects.

8. Documentation:
   - Ensure accurate and comprehensive documentation of the prescribed remedy, including dosage, administration route, and any specific instructions.
   - Record patient responses and any observed adverse effects.

9. Communication with Patient:
   - Communicate with the patient regarding the prescribed remedy, explaining the purpose, potential side effects, and any necessary precautions.
   - Confirm the patient's understanding and address any concerns.

10. Follow-Up:
    - Schedule follow-up appointments to assess the patient's progress.
    - Adjust the treatment plan as needed based on ongoing evaluation.
11. **Collaboration with Healthcare Team:**
   - Coordinate with other healthcare team members, such as pharmacists and nurses, to ensure seamless administration and monitoring.

12. **Emergency Response Plan:**
   - Develop and communicate an emergency response plan in case of adverse reactions or unexpected events during or after administration.

13. **Adherence Monitoring:**
   - Implement measures to monitor and promote patient adherence to the prescribed remedy.
   - Provide support and education to address potential barriers to adherence.

14. **Continuous Learning and Improvement:**
   - Stay updated on new research, medications, and treatment modalities.
   - Use feedback and outcomes data to continuously improve prescribing practices.

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5. **Methodology**

Use-case diagram for the Remedy application:

![Use-case diagram](image)

**Explanation of Use Cases:**

1. **Log In:**
   - The user logs into the ReMedi application to access personalized features.

2. **Search for Medicines:**
   - Authenticated users can search for medicines based on various criteria.

3. **View Medicine Details:**
   - Users can view detailed information about a specific medicine, including dosage, side effects, and instructions.

4. **Add Medicine to Cart:**
   - Users can add selected medicines to their shopping cart for later purchase.

5. **Proceed to Checkout:**
   - Users can proceed to the checkout process to review and finalize their selected medicines.

6. **Confirm Order:**
   - Users confirm their order, providing necessary details for delivery and payment.

7. **View Order History:**
   - Users can review their past orders and track order history.

8. **Log Out:**
   - Users log out of the ReMedi application.

This use-case diagram provides a high-level overview of the interactions between users and the ReMedi application, emphasizing key functionalities related to medicine selection, purchase, and order management. Keep in mind that the actual system might have additional features and use cases depending on its specific requirements and functionalities.

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6. **Conclusion**

In conclusion, developing and implementing a comprehensive remedy system for medicine, as illustrated in the ReMedi application, is crucial for enhancing healthcare experiences and outcomes. The systematic approach outlined in the algorithm and use-case diagram emphasizes user-centric design, efficiency, and safety considerations throughout the medicine lifecycle, from identification and prescription to administration and monitoring.

The algorithm for administering remedies incorporates best practices in patient assessment, medication selection, and monitoring, ensuring that healthcare providers make informed and personalized decisions. Collaboration with the broader healthcare team, clear communication with patients, and continuous learning are integral aspects of this process, contributing to a holistic and patient-centered approach to healthcare.

On the user side, the reuse of medicines, as discussed in the reuse algorithm, introduces a strategic approach to finding new therapeutic uses for existing drugs. Leveraging data mining, computational approaches and collaborative efforts can streamline the identification and validation of repurposed medications, potentially offering more accessible and cost-effective treatment options.
The ReMedi use-case diagram illustrates the user interactions with the application, emphasizing key functionalities such as searching for medicines, viewing details, and managing orders. The seamless integration of these features aims to provide a user-friendly and efficient platform for individuals seeking remedies, contributing to a positive and empowering healthcare experience.

In summary, a well-designed remedy system considers the complexities of medicine administration, repurposing, and user interactions. By incorporating evidence-based practices, embracing technological advancements, and fostering collaboration between healthcare providers and patients, such a system can contribute to improved healthcare outcomes, patient satisfaction, and overall efficiency in the delivery of medical remedies.

References

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