Reverse flows within the Pharmaceutical Supply Chain: a classificatory review from the perspective of end-of-use and end-of-life medicines

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Highlights

A classificatory literature review on medicines reverse flows is performed.

Excessive production/demand uncertainty jeopardize medicines reverse flows.

Cordination of the forward supply chain is pivotal for medicines reverse logistics.

Green chemistry is a form of circular economy in pharmaceutical supply chain.

Failures in monitoring of prescriptions hinder the circularity of medicines.

Circular economy of medicines requires deeper investigation as business opportunity.

List of acronyms

CE – Circular Economy

CLSC – Closed Loop Supply Chain

DO - Donations

EOL-M – End-of-life medicines

EOU-M – End-of-use medicines

EOU/EOL-M – End-of-use/end-of-life medicines

GSCM – Green Supply Chain Management

PSC – Pharmaceutical Supply Chain

RL – Reverse Logistics

SCM – Supply Chain Management

SSCM – Sustainable Supply Chain Management

Abstract

The Pharmaceutical Supply Chain (PSC) is responsible for considerable environmental and product-value impacts. However, studies on the reverse flows of PSC do not capture the diverse routes of end-of-use and end-of-life medicines (EOU/EOL-M) and how the constraints in the forward supply chain processes and operations impact such reverse flows. This research proposes a classificatory review in which three categories of reverse flows are identified: donations, Reverse Logistics (RL) and Circular Economy (CE). Donations are characterized by explicit philanthropic acts involving corporate reputation or by emergency humanitarian action. RL is boosted by regulatory issues and restricted by business imperatives of the PSC. CE is characterized by informal loops of not expired medicines, mainly due to health professionals' initiatives (although this may not be clear to participants). This classification emerged from content analysis of 2,622 references found in six databases, from which 127 were selected. Three questions guided the review in each category: (i) what are the elements of the forward PSC processes that impact PSC reverse flows?; (ii) in what stages of the PSC are the reverse flows identified?; (iii) what does the academic literature recommend for improving PSC reverse flows? The literature shows that excessive amounts and inappropriate types of medicines hinder donations. Inventory planning and quality control problems are the main difficulties for medicines RL. The circularity of EOU-M is affected significantly by frequent changes of patient therapies and health conditions, and by failures of healthcare agents in monitoring prescriptions. The proposed classification suggests that the circularity of not expired medicines is not yet researched in the field of logistics, supply chain and procurement, and it is scarcely considered in engineering, and business and management areas, which evokes a call for future research agenda.

Keywords: Pharmaceutical Supply Chain. Medicines wastes. Reverse flows. Reverse Logistics (RL). Circular Economy (CE).

8,558 words, with the Abstract

8,271 words without the Abstract

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Abstract

The Pharmaceutical Supply Chain (PSC) is responsible for considerable environmental and product-value impacts. However, studies on the reverse flows of PSC do not capture the diverse routes of end-of-use and end-of-life medicines (EOU/EOL-M) and how the constraints in the forward supply chain processes and operations impact such reverse flows. This research proposes a classificatory review in which three categories of reverse flows are identified: donations, Reverse Logistics (RL) and Circular Economy (CE). Donations are characterized by explicit philanthropic acts involving corporate reputation or by emergency humanitarian action. RL is boosted by regulatory issues and restricted by business imperatives of the PSC. CE is characterized by informal loops of not expired medicines, mainly due to health professionals' initiatives (although this may not be clear to participants). This classification emerged from content analysis of 2,622 references found in six databases, from which 127 were selected. Three questions guided the review in each category: (i) what are the elements of the forward PSC processes that impact PSC reverse flows?; (ii) in what stages of the PSC are the reverse flows identified?; (iii) what does the academic literature recommend for improving PSC reverse flows? The literature shows that excessive amounts and inappropriate types of medicines hinder donations. Inventory planning and quality control problems are the main difficulties for medicines RL. The circularity of EOU-M is affected significantly by frequent changes of patient therapies and health conditions, and by failures of healthcare agents in monitoring prescriptions. The proposed classification suggests that the circularity of not expired medicines is not yet researched in the field of logistics, supply chain and procurement, and it is scarcely considered in engineering, and business and management areas, which evokes a call for future research agenda.

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Introduction

A Pharmaceutical Supply Chain (PSC) is defined as a "combination of processes, organizations and operations involved in the development, design and manufacturing of useful pharmaceutical drugs" (Singh et al., 2016: 1). It is one of the most complex supply chains, as it relates to the life and the health of individuals (Schiel, 2018), supporting high levels of risks, uncertainties and significant asymmetries in information flows throughout the chain (Papalexi et al., 2014). PSC brings together thousands of different stakeholders with diverse objectives (Halabi and Gostin, 2015), such as, raw material producers, the pharmaceutical industry itself, distributors, health agents (hospitals, clinics, physicians, insurance health representatives), third party operators, retailers, and customers/patients. The pharmaceutical industry is in the mainstream of the healthcare sector (Urias, 2017). In global terms, it earns revenues over US$ 825 billion, with average growth of 4% to 6% per year (Bravo and Carvalho, 2015). The PSC is also targeted by the UN Millennium

Development Goals due to its complex interfaces with environmental impacts (solid waste and wastewater generation from incorrect discharges), human wellbeing (increased aging and demographic change that lead to escalating dependency on medicines), and social equality aims (contrasting with lack of access, high prices and losses in supply chains).

The literature on SCM reverse flows is very recent (Schenkel et al., 2015), and it is associated with terms such as Sustainable Supply Chain Management (SSCM), Green Supply Chain Management (GSCM), and Closed Loop Supply Chain (CLSC) (Gurw et al., 2015; Xin, 2010). SSCM, proposed as a theory by Pagell and Wu (2009), as a framework by Dubey et al. (2017), and as measurable indicators by Beske-Janssen et al. (2015), is the integration of sustainable goals in a supply chain (Nassir et al., 2016; Roy et al., 2018). GSCM relates to the the integration of environmental thinking throughout the supply chain (Kumar and Kant, 2015; Fang and Zhang, 2018). SSCM is associated with governance and social responsibility, and GSCM with a theoretical approach for reduction of the negative environmental impacts in a supply chain (Batista et al., 2018; Jayaram and Avittathur, 2018). However, both SSCM and GSCM are weakly developed as theories (Toublic and Walker, 2015; Dubey et al., 2017). Instead, they are mostly realized as practices as Reverse Logistics (RL) or Circular Economy (CE) – the latter also being associated with Closed Loop Supply Chains (CLSC) (Govindan and Soleimani, 2015; 2017; Xin, 2010).

RL refers to the recovery and racapture of the value of goods once they are deemed useless by a consumer, or lose functional characteristics that hinder their appropriate or safe use (Agrawal et al., 2015). RL practices involve reuse, repair and remanufacturing (Bouzon et al., 2016; Bouzon et al., 2018; Govindan and Bouzon, 2018). Reuse is using a functional component from a retired assembly. Repair is bringing damaged components back to a functional condition, and remanufacturing is a transformation of used units, components or parts to units that satisfy exactly the same quality and other standards as new units (Zeqiang and Wenming, 2006). Nonetheless, this sequence depends on the type of the targeted product – whether more or less perishable, more or less complex, and so on (Beh et al., 2016). RL does not necessarily involve closed loops. In the PSC, for instance, RL is usually taken as an activity through which wholesalers or providers collect the pharmaceutical wastes and transport them to manufacturers or places for disposal (Saravanan and Kumar, 2016; Singh et al., 2016). Although a large number of RL studies on PSC have been published, they focus basically on operations of collecting unwanted medicines from pharmacies and hospitals (Franco and Alfonso-Lizarazo, 2017).

CE promotes reduction, reuse and recycling of resources in a supply chain through cleaner production principles – whose main premise is the avoidance of wastage. A “circular economy is an economy constructed from societal production-consumption system that maximizes the service produced from the linear nature-society-nature material and energy throughput flow” (Korhonen et al., 2018: 40). Differently from RL, strongly addressed to business processes, CE looks to reverse flows in a way that promotes a win-win situation in economic, societal and environmental aspects (Genovese et al., 2017). While RL associates environmental and financial revenues, it does not necessarily bring social benefits (Lai et al., 2013). Therefore, RL is taken as a limited version of CE (Geisendorf and Pietrulla, 2018).

Even considered “superficial and unorganized” (Korhonen et al., 2018: 37), with “vague boundaries” (De Jesus et al., 2018: 3021), and devoid of unified theory (Fischer and Pascucci, 2017), the concept of CE is framed at a deeper level than the RL idea, resonating as recirculation of resources/energy, multilevel approach and ways in which society

innovates (Prieto-Sandoval et al., 2017) while re-signifying new forms of uses of goods (Reike et al., 2018).

CE is based on closed loop systems (Urbinati et al., 2017) and on extended value use instead of value exchange, therefore it aims at disentangling ecology and economy (Bernon et al., 2018). In the PSC, CE could be framed in terms of keeping EOU-M as long as possible in the economic and social cycle of use. This is more difficult than EOL-M RL. In fact, one of the barriers for CE is the complexity of the product management in reverse flows of aspects such as quantities, quality, time, pace of returns (Bressanelli et al., 2018), and health concerns (Govindan and Hasanagic, 2018).

Although reverse flows has been receiving increased attention in PSC (Narayana et al., 2014 a; 2014b; Kumar et al., 2009), it it does not capture the complexity of events and relationships related to EOU-M and EOL-M. Basically, aspects involved in planning (Serrou et al., 2014), procurement (Sanderson et al., 2015), price formation (Schiel, 2018), innovation costs (Singh et al., 2016) and other upstream coordination operations (Beh et al., 2016; Chen et al., 2018) are detached from losses and wastage in this supply chain. It also takes place through collaboration between agents (Daugherty, 2011), in vertical and horizontal directions (Soosay and Hyland, 2015), and in inter or intraorganizational dimensions (Rebs et al., 2019). Research on medicines returns are scattered through the literature under labels as diverse as: medicines/drugs donations programs (Nicoli et al., 2018) and its environmental and human implications; Reverse Logistics (Campos et al., 2017); Circular Economy (Zhou and Zhang, 2007); and Closed Loop Supply Chain (Amaro and Barbosa-Póvoa, 2008).

The PSC suffers from a lack of unified theoretical approaches, which hinders the assessment of its flaws and opportunities for improvement (Halldorson and Kotzab, 2015). It is a common gap in the field of SCM, which evolved from inventory management to production and plannning control, and becoming a specific focus of study since the 1990s. PSC is usually studied from its components, as stakeholders, flows, relationships, coordination, value, efficiency, and performance (Ahi and Searcy, 2014) rather than under a specific theory. This gap is especially relevant in regards to the reverse flows of this chain, and has motivated the look for a classification to better understand diferences in reverse activities.

Considering that the gaps in forward processes in PSC can affect the reverse flows – the forms and paths through which used medicines (EOU or EOL) are managed after their distribution to patient – this paper undertakes a classificatory review of the literature on PSC reverse flows. It aims at addressing the following questions: (i) what are the elements of the forward PSC processes that impact PSC reverse flows?; (ii) in what stage of the PSC are the reverse flows identified?; (iii) what does the academic literature recommend for improving PSC reverse flows? All these questions are framed for the context of EOU-M and/or EOL-M rather on all products within the PSC.

The paper is organized as follows. In the next section, the methodological design is described and justified; in the third section; results are presented and discussed in two parts: descriptive analysis of reviewed documents, and content analysis for each category. Conclusions and recommendations for future studies are presented in the fourth section.

2 Methodological approaches

This research adapted methodologies already employed in seminal work (Cormack, 1971) and recent work (Littel, 2018) of qualitative-classificatory review combined with review procedures offered by the classical academic literature on sustainability in SCM (Seuring et al., 2005; Seuring and Müller, 2008).

Cormack (1971) recommends classificatory review as a means for organizing and solving questions. Based on Littel (2018), a classification of reverse flows of EOU-EOL-M is proposed taking in to consideration three categories: Donations, RL, and CE. RL and CE are presented in academic literature, according the concepts exposed in the Introduction section. Donations, on the other hand, can be considered an empirical category because they are not consensually conceptualized.

For the sake of clarity, donations, RL, CE were all associated with SSCM, whose aim is to input principles of sustainability (as corporate social responsibility) to SCM. RL and CE were both associated with GSCM, as they keep green principles (such as wastage avoidance) in the supply chain. CE was additionally associated with CLSC, because it seeks the maximum circulation of goods in a supply chain, in order to accomplish both, waste avoidance and social benefits. Figure 1 shows the considered scheme for each category and their respective links with SCM theories/frames associated with sustainability.

<Figure 1 here>

Littel (2018) recommends that classificatory reviews support focus, goals, and coverage. The focus of this research are the reverse flows of EOU-EOL-M in three categories, and the goals are the answers for the research questions posed in the Introduction. The coverage refers to the procedures of collecting the corpus of the literature review: databases, established criteria for the types of recovered studies, selected keywords, and comprehensiveness in time. A set of six databases was consulted: with Web of Science (WoS), Emerald, Wiley, Taylor & Francis, and Science Direct all interrogated across all years, and Google Scholar interrogated from 2014. For WoS, we considered only the databases of health sciences as PubMed, Medline, SciELO, and CAB Abstracts, which includes Global Health and other similar meta databases related to health issues. We did not consider other metabases within WoS such as patents directories and others not related to health. For Google Scholar, we have limited the search from the last five years (including 2019) because of the excessive amount of results and high level of duplicates with other databases already included in the scope of this review. The search was carried out using the following key expressions: “pharmaceutical supply chain” and “drug(s)/medicine(s) donation(s)” (for the first search); “drug(s)/medicine(s) donation(s)” and “reverse logistics” (for the second); and “drug(s)/medicine(s) donation(s)” and “circular economy” and “medicines wastage” (for the third). Such key expressions were repeated for each database.

From the overall searches, there were recovered a set of documents, mainly peer reviewed articles. A first filter was applied in order to eliminate duplicated articles. Then, for the remaining references, the titles and the abstracts were analysed to evaluate whether they could provide answers to the three research questions. If so, the respective references were selected as the definitive research corpus.

Final results included mostly peer reviewed papers, along with a small proportion of international congress papers and PhD dissertations. The selected references were checked and organized in order to avoid redundances and eventual losses of relevant

content. Results systematization and analysis followed two strands: a descriptive and a content analysis, according to Seuring et al. (2005) and Seuring and Müller (2008).
For both types of analysis, the seminal works of Seuring et al. (2005) and Seuring and Müller (2008) were partially adopted. According to these authors, the literature review for SCM must be explicit, systematic, reproducible, and based on theories. In the current research, theories on reverse flows of EOU-EOL-M were not identified in the academic literature. That is why a previous classificatory review (shown in Figure 1) was structured, following, as best as possible, studies on SSCM, GSCM, and CLSC associated with donations, RL and CE of medicines, as indicated in the Introduction.
For the descriptive analysis, the following information was retrieved: number total of selected references published by year; more representative countries in which the research is carried out for each considered category; methodologies employed in the studies; and number of references by disciplinary field of the selected studies. This last item of the descriptive analysis was amplified in Appendices A, B, and C, where the wide range of journals involved in the results is listed. The overall results of the descriptive analysis was then discussed.
For the content analysis, the inductive method (categorization after reading the selected documents) was employed, which means that the categories emerged from the content. Nevertheless, this process was guided by the research questions posed in the introductory session of this research. Therefore, the inductive method outlined by Seuring et al. (2005) and Seuring and Müller (2008) was adapted. For donations, the results covered: (i) constraints (ii), where it occurs in the supply chain; (iii) recommendations for improvement. For RL, the content analysis covered: (i) barriers, drivers/opportunities, alongside reviews, models, and specific constraints, as emerging subjects; (ii) where it occurs in the supply chain; (iii) recommendations for improvement. Finally, for CE, there were identified contents as CE and CLSC; CE as epistemical view of social responsibility; CE upstream in the chain (green chemical); CE downstream in the chain (packaging and bioeconomy), reusing and wastage avoidance; (i) constraints, (ii) where it occurs in the supply chain; and (iii) recommendations for improvement.
The design employed for the methodological procedures is depicted in Figure 2.

<Figure 2 here>

3 Results – Description and Classification

The searches identified 2,622 documents, which were mainly peer reviewed articles. After a first filter applied to eliminate duplicated articles and to read the titles and abstracts of the remaining articles, 127 references were selected – 12 for the category donations; 81 for RL, and and 34 for CE. Table 1 presents details of the quantitative results of the review.
The categorization into donations (DO), RL and CE followed the criteria detailed in Figure 1. Donations were considered acts of any person - mainly of corporations and humanitarian organizations, carried out for philanthropy or corporate social responsibility aimed at providing medicines for needy persons. RL were classified as reverse flows of PSC members, mainly distributors, retailers, consumers, in order to accomplish regulatory purposes seeking economic gains. CE included recirculation of not expired medicines, mainly on the initiative of health professionals and consumers to fulfill needs and avoid wastage. Under such criteria, it was possible to separate and classify the results.

< Table 1 here>

3.1 Descriptive analysis

This analysis, with respect to the framework suggested by Seuring et al. (2005) and Seuring and Müller (2008), refers to the following information: total number of selected references published by year for each category (Table 2, Figure 3); more representative countries in which the research is carried out for each category (Table 3, Figure 4,); number of references by the main disciplinary fields of the selected studies (Table 4, Figure 5); journals of the publications by category (Appendices A, B, and C); and methodologies employed in the studies (Table 5, Figure 6).
From these data, it is possible to realize that the number of publications on donations has low variability, but for RL and CE it shows considerable increase in recent years. For RL, a peak was identified in 2014, with stabilization in the following years. For CE, an increase from 2017 is apparent. Table 2 and Figure 3 present the details on the chronology of the selected publications.

<Table 2 here>
<Fig. 3 here>

In the current study, countries were included with at least two references in at least one of the considered categories. It is possible to see that research on medicines donations is carried out mostly in the US and UK. The situation is similar for RL and CE. The US has the highest number of studies on RL, while UK has the highest number on CE (Table 3, Figure 4). CE is scarcely researched in the US, which can indicate a contrasting cultural reality in the way the American and the British society deal with EOU/EOL-M.

<Table 3 here>
<Figure 4 here>

From the peer reviewed identified journals in which the research on donations, RL and CE was published, those from the pharmacy field are dominant, followed by those from the health, the logistics, supply chain and procurement fields. Donations research is mostly published in journals of the health field; RL in journals of logistics, supply chain, procurement, and engineering areas; CE studies are predominant in journals of pharmacy. Table 4 and Figure 5 show the distribution of the publications by knowledge field. The lack of CE research published in journals of logistics, supply chain, procurement and engineering fields is noticeable, which can indicate that discussion on circularity of medicines is out of the scope of those journals. Conversely, CE of medicines is widely spread in journals of pharmacy, which raises the possibility that professionals in this field are closer to the idea of medicines loops than supply chain managers or engineering professionals. In this sense, circularity seems more usual for patients and health professionals, regardless of whether they intend to practice the principles of CLSC or to simply put in circulation a medicine surplus, avoiding wastage and adjusting the right dose and right medicine to the patients' needs. Appendices A, B, and C show in details the journals considered for this research.

<Table 4 here>
<Figure 5 here>

Regarding the methodologies employed, qualitative and survey studies are dominant (Table 5, Figure 6). Quantitative methods, case studies and literature review are most commonly employed in RL research, whereas surveys are usual for CE. This can indicate that RL has more maturity than CE research when related to the subject of EOU/EOL-M.

<Table 5 here>
<Figure 6 here>

3.2 Classificatory analysis

The classificatory analysis is based on a previous systematization of the reviewed documents under three categories: Donations, RL, and CE. As argued in the Introductory section, reverse flows of goods, including medicines, suffer from the lack of a sound theoretical basis for its analysis. In the case of EOU/EOL-M donations, RL, and CE, all such categories reflect the ideas of SSCM, which are associated with governance and social responsibility. RL and CE, especially, reflect GSCM frameworks, that rely on the environmental aspects of the reverse flows. It means that under GSCM principles, the returns of medicines, for correct disposal (RL), or for reuse (CE), are both associated with wastes avoidance. The circularityof used and not expired medicines corresponds to the idea of maximum harnessing of a good through successive loops of reuse, which is aligned with CLSC principles. Having such aspects in mind, the classificatory analysis was designed to answer three questions for each category: (i) what are the elements of the forward PSC processes that impact PSC reverse flows?; (ii) in what stages of the PSC are the reverse flows identified?; (iii) what does the academic literature recommend for improving PSC reverse flows? The answers, from the literature review, are provided and indicated in bold subtopics, in the following subsections for donations (3.2.1), RL (3.2.2), and CE (3.2.3).

3.2.1 EOU-M Donation Programs

Medicines donations are old philanthropic practices that probably began with journeys of physicians and nurses from developed to developing countries, based on the transport of surplus medicines (Smego Jr. and Gebrian, 1994). Such practices can improve the access to medicines in middle and low income countries (Attaran, 2004), but there is little impact assessment or reported lessons of these initiatives (Jenny et al., 2016).

Poor coordination hinders the efficacy of many such humanitarian programs (Dolinskaya et al., 2018), even at small scales. Donations are also jeopardized due to lack of capacity of health professionals (Chukwu et al., 2016).

There are several forms of medicines donations, and the motivation and outcomes of such types of initiatives are controversial. Humanitarian causes (wars, epidemics) are the pivotal reasons behind donations (Collins, 2004; Colatrella, 2008). One of the main criticism of medicines donations is the mismatch between what poor communities need and what is given (Jenny et al., 2016; Guilbaud, 2018; Nicoli et al., 2018). A typical example of negative results associated with medicines donations is the case of the Bosnia

and Herzegovina war (1992-96), during which around 60% of the given medicines were misappropriated (Beckmans et al., 1997). It motivated the WHO to issue guidelines for best practices in medicines donations, emphasizing the responsibilities of the responsible parties (WHO, 2010).
Beckmans et al. (1997) assessed data on 12 multilateral and non-governmental organizations involved in medicines donation, and found four critical situations: useless products (irrelevant to the local epidemiological and clinical context), unusable (EOL-M at the time of arrival or soon afterward), unidentifiable (not labelled or labelled in unknown language), and damaged (in transportation and storage) medicines. Bero et al. (2010) analyzed academic literature of medicines donations from 2000 to 2008, and found reports of 96 incidents, mainly related to the supply chain transportation and warehousing.
- **Forward flows that affect the reverse**
In the current review, the main identified elements of the forward supply chain that affect donations are: excessive production, demand uncertainty and products quality (Attaran, 2004; Dolinskaya et al., 2018); and package/labelling, transportation and storage failures (Beckmans et al., 1997). Appendix D brings more details on this topic.
- **In what stages of the PSC donations occur**
It is difficult to precisely identify in what part of the PSC donations take place. Reviewed studies (see Appendix E) indicate that it happens between diverse sources and end users (Bero et al., 2010; Nicoli et al., 2018). From the reading of the selected papers, a depiction is provided in Figure 7, in order to indicate answers to this question

<Fig 7 here>

- **Recommendations for improving EOU-M donations**
The review found that collaboration between stakeholders (Kale et al., 2013; Guilbaud, 2018) and adherence to best practices guidelines (Beckmans et al., 1997) are the core suggestions for improving EOU-M donations. Recommendations of each reviewed document are expressed in the Appendix F.

3.2.2 EOU/EOL-M Reverse Logistics Programs

EOU/EOL-M can return to the economic cycle through reverse logistics, which "involves the collection of goods from end consumers, sorting of goods received, disposal of goods and retrieval of components at various stages in the supply chain and remanufacturing processes" (Kwateng et al., 2014:17). From the literature review, it is possible to identify four main tendencies in EOU/EOL-M studies: barriers related to planning, operational aspects, costs, public policies, and culture; drivers and opportunities for improvement; models; and review studies. Such barriers are herein presented as answers to the first research question of the present study (elements of the forward PSC that impact reverse flows). The loops of the supply chain in which RL occurs are indicated for filling the second question. And the identified opportunities and drivers, including models and reviews, are described as answers to the third research question (recommendations for improvement).
- **Barriers in the forward PSC that affect RL**
Barriers to EOU/EOL-M RL are from several types. Regarding planning and operational barriers, 11 aspects of the forward PSC that impact RL were identified: extension of the

supply chain, that causes difficulties for coordination between stakeholders; difficulties for management of flows/lack of flexibility; quality control problems (including packaging); inventory/production planning problems; excessive production; lack of specific medicines availability; procurement problems; storage problems; delivery delays; logistics inefficiency; high perishability/low shelf life of medicines. Many coordination problems of the PSC that end in reverse flows start as demand and inventory failures in forward processes (Singh et al., 2016; Lücker and Seifert, 2017; Abbas and Faroquie, 2018; Lima et al., 2018), or in storage and transportation (Bolineni, 2016; He et al., 2016), resulting in lack of control over EOU/EOL-M (Mustafa and Potter, 2009; Balbino and Balbino, 2011; Kwateng et al., 2014).

Costs (of operation, distribution, and transportation) and prices (for consumers) are deemed relevant barriers of the forward PSC that affects RL (Mwencha et al., 2017). Costs can be negatively affected by the presence of third party agents (Rossetti et al., 2011), diversion of medicines (Nakyanzi et al., 2010; Romero, 2013), counterfeiting (Ali, 2015; Mackey and Nayyar, 2017), difficulties to monitor the supply chain, given the extension and diversity of items (Kongar et al., 2015; Mackey and Nayyar, 2017; Narayana et al., 2019), and perishability (Subzwari and Nasir, 2015).

Public policies barriers of the PSC that jeopardizes RL are: lack of transparency in prices, that could be avoided through the adoption of new technologies of traceability (Ding, 2018); lack of regulatory frames (Khan and Subzwari, 2009; Falqueto and Kligerman, 2013); defective intellectual protection (Cameron, 2009; Thepsatidsilph, 2015; Urias, 2015); informal trade/counterfeiting (Li and Hamblin, 2016). Counterfeiting drugs are those that contain "no active ingredient, an incorrect amount of active ingredients, incorrect ingredient, and/or unapproved labeling and packaging" (Ziance, 2008: 71).

Bueno et al. (2017) identify institutional gaps involving producers, distributors, retailers, and consumers in PSC that prevent correct procedures for RL taking place. Problems of traceability in PSC is an institutional difficulty also described by Enyinda and Szmerekovsky (2008) and Enyinda and Tolliver (2009), and by Schiel (2018). Cultural constraints are spread all over the PSC, and have pivotal relevance for impeding RL processes.

The identified aspects of cultural barriers are: lack of consumers' awareness (El-Hamamsy, 2011; Kifli et al., 2018); lack of innovative culture in downstream parts of the PSC for supporting RL (Khan and Subzwari, 2009; Law et al., 2014); lack of information/transparency between physicians and patients or prescription problems (Trueman et al., 2010; Elliott, 2013); lack of training/capacity building of health professionals (Tong et al., 2011); patient behaviour problems, such as non adherence to medicines, treatment abandonment, and careless attitudes (Xie and Breen, 2012; Kagashe et al., 2014; Vogler et al., 2014; Pereira et al., 2017; Kelly et al., 2018). Appendix G shows in details all such barriers and associated studies.

In summary, inventory/production planning appears as the main constraint of the forward PSC that impacts RL (Nematollahi et al., 2017a; 2017b; Narayana et al., 2019, and other authors listed in Appendix G, column 4). The second constraint is the extension of the supply chain and consequent difficulties of coordination between stakeholders (Masoumi and Nagournay, 2012; Li and Hamblin, 2016; Weraikat et al., 2016b, and other authors cited in column 1 of Appendix G).

In what stages of the PSC RL occurs

RL occurs mainly between patients/consumers and pharmacists (Schiel, 2018, and others), and after the final consumption (Campos et al., 2017, amongst others). Appendix

H provides the full list of authors that confirm this situation. Some studies indicate specifically four points of RL concentration. One lies between industrial internal flows, indicating quality assurance problems (Cameron et al., 2009; Serrou et al., 2014; Xie and Breen, 2014; Li and Hamblin, 2016; Imran et al., 2018). Another is between pharmacists and industry, probably referring to returns of EOL-M or recalls (Nakyanzi et al., 2010; Breen and Xie, 2015; Kamba et al., 2017; Nematollahi et al., 2017 a; 2017b, for example). A third one is found between pharmacies and third party agents, also for returns or recalls (Kongar et al., 2015; Rolewicz-Kalińska, 2016; Singh et al., 2016; Weraikat et al., 2016 a; 2016b). The fourth is identified between EOU-M donators, from several sources, and end users (Trueman et al., 2010; Blackstone et al., 2014; Kagashe et al., 2014; Bekker et al., 2018; Kifli et al., 2018) but out of the context of reusing and rather framed as wasted medicines. Evidence of direct RL between distributor and industry, and between distributor and third parties, was not identified in the literature. Figure 8 provides a detailed idea on the stages of the PSC in which RL occurs.

<Fig. 8 here>

Opportunities and drivers (recommendations) for RL improvement

Opportunities for RL improvement start from the forward chain, with coordination among stakeholders on the right quantities, distribution places and times (Kraiselburd and Ydav, 2013; Pinto et al., 2014) and affordable prices (Cameron et al., 2009; Baxerres and Hesran, 2011; Schiel, 2018), or with the adoption of cleaner production strategies (Li and Hamblin, 2016). Governmental drivers can boost medicines RL. Examples are the extended responsibility policy for the PSC implemented in Portugal (Niza et al., 2014), the attempts to develop metrics for RL in India (Aghalaya et al., 2012), and the recommendation for legislation improvement in China (He et al., 2016).

Ritchie et al. (2000) reported the benefits of EOU/EOL-M RL in 28 UK hospitals, with potential for significant economic savings. Breen and Xie (2015) also reported drivers for medicines RL in public hospitals. In Pakistani pharmaceutical industries, Khan and Subzwari (2009) found that improvements in the reverse flows could save at least 10% of the US$ 5 billion costs of the estimated system. Medicines procurement improvements can be associated with RL processes bringing benefits to the whole supply chain (Foster, 1991; Nakyanzi et al., 2010; Xie and Breen, 2012, 2014; Sanderson et al., 2015). Appendix I brings a list of recommnedations for RL improvements, according to the reviewed studies.

Reviews and its contributions

De Brito et al. (2005) reviewed more than 60 studies on the complex RL relationships, including PSC. In another review, Narayana et al. (2014b) concluded that PSC has three levels of indirect interaction: among governmental bodies, healthcare purchasing groups, and healthcare providers. One of the most comprehensive reviews on medicines RL was carried out by Campos et al. (2017). They screened studies from 1996 to 2015, and concluded that a systemic set of planning and action, involving all the participants of the supply chain, is lacking in the PSC reverse cycle. While earlier studies were focused on toxicity, water contamination and risk assessment of incorrect medicines disposal, more recent studies address the greening of the supply chain. Lima et al. (2018) reviewed the literature on counterfeit drugs and how to tackle this problem. Such reviews, therefore, indicate the need for more horizontal integration and collaboration for RL in PSC.

Models for operations improvement

Many scholars propose RL models for EOU/EOL-M. Amaro and Barbosa-Povoa (2009) analyzed different scenarios regarding product demands, price and uncertainties in a Mixed Integer Linear Programming. In an early study, these authors have designed sequential planning and scheduling of supply chain structures with reverse flows (Amaro and Barbosa-Povoa, 2008). Kumar et al. (2009) employed the DEMAIC (Define, Measure, Analyse, Improve, Control) approach for analyzing PSC in recalls. Pribluda et al. (2014) developed a three level model for avoiding counterfeit medicines. A framework for medicines RL linked to RFID was developed by Kongar et al. (2015), although this technology has already been recommended since the previous decade in this supply chain (Chao et al., 2007; Wyld and Jones, 2007; Tzeng et al., 2008). A model for EOL medicines disposal, after a literature review, is designed by Kumar and Saravanan (2016). Ding (2018) proposes the introduction of 4.0 manufacturing in PSC for improving sustainability.

Rolewicz-Kalińska (2016) proposed a framework for efficient medical operation of medical wastes. Moslemi et al. (2017) developed a comprehensive, multi-objective mathematical model in the healthcare supply chain considering quality and green concepts. Weraitak et al. (2016a) suggested a valuation system for second-hand medicines (EOU/EOL), stratified acording to the term of expiry. In another study, Weraikat et al. (2016b) indicated avenues for assessment of costs for collecting, reusing, recycling, and final disposal of EOU/EOL-M. Nematollahi et al. (2017a) argue that in improving the balance of stocks in forward logistics, it is possible to avoid wastes through simultaneous coordination of the medicines retailer's service level and the respective supplier's visit interval in a two-echelon PSC. Collaborative support between supplier and retailer is pivotal for achieving a better performance in the PSC (Nematollahi et al., 2017b). Nevertheless, distributors and retailers have different interests, so the balance of flows can be hindered (Narayana et al., 2014b; Nematollahi et al., 2018). Finally, Imran et al. (2018) proposed a medicine supply chain model for an integrated healthcare system considering time, quality and costs, and the perspective of consumers, which is when RL starts. These diverse models indicate that scholars are trying to optimize structures and means for RL in PSC, although they get limited by the issues of extension of the supply chain and volatility in collaboration.

3.2.3. Circular Economy (CE) and CLSC involving EOU-M

CE is not explicitly referenced in the PSC literature, although the idea of circularity or CLSC is presented as reuse (Alhamad et al., 2018; Connelly, 2018), return of medicines (Daniszewsi et al., 2002; AlSamanhodi et al., 2017) and even in the market of medical devices (Bange and Morgan, 2018). Søndergaard et al. (2006) argue that the practice of medicines returns for reuse can reduce overall health costs and time at hospital, although with no positive impacts for medicines market prices.

Medicines CE appears indirectly in reference to the organic chemical industry, having pharmaceuticals as a branch (Zhang, 2017), and to green chemicals (Andrews et al., 2010; Jimenez-Gonzalez et al., 2011; Koenig et al., 2018), in the upstream of the PSC. Trends in CE retrieved from the literature review can be classified as those generally and those strictly linked to the PSC. Usually, CE approaches advocate a new epistemical view of social responsibility. Strictly, CE is identified in both upstream and downstream of the PSC, as green chemistry in the former case, and as packaging and bioeconomy tendencies

in the latter. A third strict approach is EOU-M wastage reduction or avoidance. These findings were organized as follows, in order to answer the research questions with respect to CE.

Barriers to the forward PSC that affect EOU-M CE

CE is a type of epistemic view of sustainability, which integrates cleaner production and social responsibility principles. In fact, welfare disconnected from the traditional linear economy (production-consumption) represents a new perspective for industrial sectors and its supply chains (Hens et al., 2018). Alexandru and Tasnadi (2014) state CE as a blue economy, where the consumption of the resources go beyond the usual product/services pushing. A non-waste society (Hesmati, 2015), one of the principles of the CE, implies loops that keep goods circulating as much as possible through integrative strategies (Wang et al., 2018). It includes substitutable products (Hosseini-Motlagh et al. (2018) and product/wastes symbiosis (Ezura et al., 2016).

CE is also represented as Logistics Social Responsibility (Mani et al., 2018) while embracing practices of corporate social responsibility (Yin and Jamali, 2016) or responsible management of the supply chain (Miao et al., 2012). It is indeed named socially responsible CLSC (Modak et al., 2018). All these nominations indicate forms of ethical practice inclusion in supply chains that surpass the idea of a reverse flow for business, as usually intended for RL.

Engaging consumers to provide easier access to medicines, for instance, is in line with CE principles (Tang, 2018). In the context of EOU-M, reusing becomes increasingly relevant, as significant quantities of medicines which are not yet expired are left over in homes, pharmacies, warehouses, clinics, hospitals, and other parts of the PSC. Such a perspective can be seen as paradoxical through a conventional business lens (van Bommel, 2018). These ethical and economic aspects are, arguably, relevant barriers for medicines circularity. Given the increasing need of new products lauchning and fierce market competition in PSC, CE seems an invisible, sometimes forgotten and even repressed process in the context of EOU-M. In the current research, the main barriers identified for medicines reuse are linked to the variability of the products' quality (Rees, 2011; Lorenzini et al., 2017, among others); to the lack of medical prescriptions monitoring (West et al., 2014; Hampson and Ottey, 2015; McRae et al., 2016), and to impasses linked to prescriptions duration versus changes in patients conditions (Taitel et al., 2012; King et al., 2018). These aspects are represented in detail in Appendix J. What is noticeable, with respect to contraints for CE of medicines, is that the literature focuses on the end of the supply chain. It exposes the constraints faced by pharmacists and other health professionals that try to harness the value of used, not expired, medicines while managing regulatory and other formal aspects of the public health sector.

In what stages of the PSC CE occurs

The circularity of EOU-M is higher between patients, physicians or other health professionals (Petty et al., 2014 and others). Between patients and pharmacists it is also very common (West et al., 2015, for example), and during or after patients' consumption (AlSamanhodi et al., 2017 and others). Appendix K presents details about the common loops of the supply chain where EOU-M circulate for reusing. Circularity seems to be higher in informal relationships, which does not mean it is disorganized (Twigg et al., 2015). Figure 9 brings a scheme with the results of the review of EOU-M CE. From this

figure, it is possible to identify the main points of the loops' concentration in the PSC for the CE of medicines.

<Fig 9 here>

Opportunities and drivers (recommendations) for CE improvement

There are several opportunities for reusing EOU-M. It is a reality through specific legislation, as adopted for return programs in 37 States of the US (Connelly, 2018), or through small initiatives in hospitals (Toh and Chew, 2016), since ethical and technical protocols are followed for avoiding risks (Alhamad et al., 2018). Nevertheless, a broad research on qualitative aspects of medicines reuse and wastage is scarce (Bekker et al., 2017; West et al., 2014). Such opportunities can be easily hindered by situations such as treatment discontinuation and dispensing of medicines in higher than necessary quantities (AlSamanhodi et al., 2017; Gyanendra et al., 2011).

According to Daniszewsi et al. (2002), campaigns on unwanted medicines disposal have existed since the 1970s, but they remain a problem. These authors analyzed eight communities regarding medicines use and concluded that longer than 30 days prescriptions and therapies change are the key causes of wastage. This is a similar finding to King et al. (2018), observing that there is no ideal frequency for issuing prescriptions, as already indicated by Taitel et al. (2012). Petty et al. (2014), on the other hand, concluded that 28 days was the maximum limit for prescriptions to prevent wastage. However, this is at odds with those who find treatment adherence seems to be better with longer prescriptions (White et al., 2010; King et al., 2018), which creates a conflict with environmental care. O'Leary et al. (2006) warns that few health experts care about the lifestyles of beneficiaries, advising them on the risks of interactions in the simultaneous use of several drugs.

Self-management strategies, changes in medical conditions and over-collection due to fear of future necessity, are causes of medicines wastage related to patient behaviour (Jesson et al., 2005; Singh et al., 2011).

Reducing wastage of medicines and improving healthcare are not necessarily opposed, but are difficult to align (Taylor 2010, 2014), especially considering the dynamics of patients response for each treatment. New technologies that identify the right medicine dosage at the right time, are alternatives for wastage of medicines (Bange and Morgan, 2018), although are not widely accessible. The opportunities for EOU-M circularity, therefore, lies mainly on the way patients and health professionals manage and value medicines that can be reused under careful supervision. It is recommended that pharmacists get as close as possible to patients in order to monitor presciptions and usage of medicines (Latif et al., 2013; Shah et al., 2014; West et al., 2014).

The drivers for EOU-M circularity are basically from upstream and downstream in the PSC. In the first case, initiatives for recycling raw materials upstream in the PSC started in the middle of the past decade by the American Chemical Society (ACS) (Andrews et al., 2010), and more than US$ 2 million have been invested in this field since then (Koenig et al., 2018). Practices, such as intensity mass control in processes (Jimenez-Gonzalez et al., 2011), are examples of the engagement of PSC in the CE principles. Cleaner production in PSC is aligned with green chemistry (Ze-hua et al., 2011).

In the second case, two situations were identified in the current review: packaging design and bioeconomy. Packaging design is crucial for avoiding wastage of EOU/EOL-M. Stringent regulation is a major force for innovation in such respects, followed by technologies of traceability (Lorenzini et al., 2017). Changes in packaging affect logistics,

market, design, and the environment. Social and ethical aspects of packaging, although becoming relevant with the aging of the population and with the rise of new needs for medical treatments, are still overlooked. Technological change in packaging occurs after, or at the same time as, the product innovation, because the costs for focussing only on packaging change are high. Schaefer and Cheung (2018) advocate the development and use of smart packages for extending the shelf-life, monitoring the freshness, and displaying detailed information about products.

Regarding bioeconomy of surplus medicines, it could be adopted as the source for some raw materials, such as phosphate (Carraresi et al., 2018) or perishable products, such as food (Frigo and Lucchini, 2018), always respecting the quality control parameters (Kane et al., 2018). The last alternative under cleaner production principles would be EOU/EOL-M destruction using techniques such as pyrolysis (De Filippis et al., 2012) for energy harnessing.

Recommendations for boosting EOU-M circularity are detailed in Appendix L, where it is clear that the main aspect is the management and monitoring of prescriptions by pharmacists or other health professionals (White et al., 2010; Shah et al., 2010, and others). Providing investments in capacity building and cleaner production initiatives in the PSC are also advised (De Filippis et al., 2012 and others).

4 Discussion, conclusions, and recommendations for future research

The comprehensive literature review, descriptive and classificatory analysis of the PSC reverse flows presented in this study casts light on the complexities of the processes and relationships that pose difficulties for a robust sustainable management of medicines that are considered wastes in this supply chain. Firstly, EOU and/or EOL-M are not common terms associated with reverse flows in the PSC. The assumption behind this research is that, due to the extended nature of the supply chain, the diversity and large number of stakeholders, and the scattered configuration of the flows in forward processes, the PSC is subject to several barriers affecting the development of reverse flows of medicines. It consequently hinders the adoption and the support of sustainable supply or green supply chain management initiatives throughout the chain, from the raw material procurement and upstream production processes through to the final use of medicines.

From the descriptive analysis, it was possible to unveil the predominance of authorship from the UK and the US in medicines reverse flows. Furthermore, it was found that journals of the pharmacy field are dominant, and that journals of logistics, supply chain, procurement, and engineering rarely give space to publications of medicines CE issues.

Although the academic studies on PSC in its reverse flows are increasing, they do not portray such flows as effective, and the bulk of specific literature relates to the restricted number of echelons in this supply chain. Research on medicines reverse flows is more robust when related to mathematical models for inventory control and collaboration between stakeholders, in the early or middle stages of the supply chain, rather than in the late stages when consumers, physicians, pharmaceutical companies and other healthcare agents play decisive but often uncoordinated roles in the destination of EOU/EOL-M. In the final steps of the downstream supply chain, successful examples tend to be small-scale and context-specific cases.

Also, the difficulty in finding studies on EOU/EOL-M in a given type of journal was evident: such studies are spread through diverse thematic sources of publication. It can indicate that the field of medicines reverse flows suffers from the lack of a sound

theoretical basis. In fact, the whole reverse supply chain management field is a recent academic and empirical construct that portrays pieces of frameworks from SSCM, GSCM and CLSC.

This research made clear the need for a previous categorization of the reviewed studies in donations, RL and CE while assuming that the diferences among such reverse flows constructs, although outlined, still needs more clarity. The assumption behind the current categorization is that SSCM serves as an umbrella for all types of medicines reverse flows, while GSCM fits more to RL and CE (as both pursue environmental aims), and CE is the only reverse flow that can support CLSC principles – such as, for instance, the attempt to maximize the harnessing of used and not expired medicines.

In the context of EOU/EOL-M, RL usually refers to collection of pharmaceutical items, mainly expired, for correct disposal, while donations and CE look for win-win situations between agents of the PSC. In this respect, donations and mainly CE are moved by ecological and ethical reasons, with the sense of maximizing use value, and are both decoupled from economic value pursued in RL. Nevertheless, donations are still strongly linked to philanthropic and social corporate responsibility of companies, or to humanitarian action for emergency situations, while CE is practiced predominantly through informal relationships of the PSC stakeholders. In contrast to donations, which do not necessarily entail orientations for medicines reuse, CE involves mainly health professionals, that supervise and try to find strategies for medicines reuse, and patients with difficulties in affording medicines and patients that lack specific knowledge on how to best manage their medical prescriptions, avoiding losses. Nonetheless, even circularity does not prevent wastage at all: it is more an ideal than a reality. Research on the number of times an EOU-M keeps circulating from owner to owner in the end of the PSC were not found under the scope of this review.

The current research posed questions on the elements of the forward chain that impact reverse flows; on the stages of the supply chain in which the reverse flows take place; and on the recommendations for improving reverse flows. In such respects, it was found that EOU-M returns are constrained mainly due to poor coordination, even at small scales, in the supply channels that are presumably designed to manage donations. Mismatches between what is donated and what is really needed by patients are the main problem. Useless, unidentified, damaged products hinder the quality of donations. Improving collaboration and adherence to specific guidelines are the recommendations for increasing donations.

Inventory/production planning problems, and the large extent of the PSC appear as the main difficulties for EOU/EOL-M RL, which occur mostly between patients/consumers and physicians or other health professionals, and after the final consumption. In contrast to donations and RL, CE is not clearly referenced in the literature in relation to EOU-M, but it is instead associated with CLSC or circularity – this latter expression being more common. The principal expressions of CE in the PSC are green chemistry, in upstream parts of the supply chain, and in new trends in packaging and bioeconomy, in downstream parts. It is possible to foresee tendencies in respect of circularity looking to studies of food supply chain CE that has in common with medicines the aspect of perishability. In this respect, CE maintains some similarities with donations, because the aim of the reverse flow is to help end users while reducing environmental impacts. CE of medicines takes place mostly between patients, physicians or other health professionals, and this type of circularity is designed as informal loops, not at all closed, because for this it would be necessary to take action to optimize the prescription systems management.

This study presents some limitations. The first one regards the difficulties in undertaking a comprehensive and, at the same time, representative academic literature review. It was necessary to combine diverse expressions in order to find significant studies in the broad scope of reverse flows in PSC. Terms, such as, "end-of-use" and "end-of-life", even when combined with "medicines" or "drugs", were not efficient for the designed purpose of the research. The second constraint is the fact that dealing with a very large and complex supply chain, results in very diverse fields of research being included in the search findings. This enriched the classification, but at the same time, made it a difficult task.
Special attention must be given to the first question that motivated this research. The fact that coordination and collaboration have appeared as the main barriers to the forward flow of the PSC that affects the reverse flows (whether donations, RL, or CE) indicates that it is very reasonable to suppose that problems of forward PSC are also the roots of reverse flow barriers in this supply chain.
For future research, it is recommended to deepen this line of investigation that tries to link factors and aspects of the forward PSC that resonate in the reverse channels. It is necessary, for instance, to design studies that can support particular hypotheses on this causal relationships in order to bring more robust evidence to test such assumptions.
From our results, we also recommend that editors of journals which embrace the topics of logistics, supply chain, procurement, and operations management (engineering), pay attention to the topic of CE as a form of reverse flow as being an important element of RL. Finally, we recommend more studies that can shed light on how the circularity of medicines can be made more visible and spread through all stages of the reverse PSC. Particularly, we recommend the investigation of how health professionals (mainly related to pharmaceuticals) have or have not been prepared to deal with the practices of the CE since their academic formation, and how they can improve their contribution to reduce medicines wastage in reverse flows. It is particularly necessary to increase the amount and the quality of studies on capacity building and knowledge management of such professionals considering that the CE cannot be limited to durable goods.

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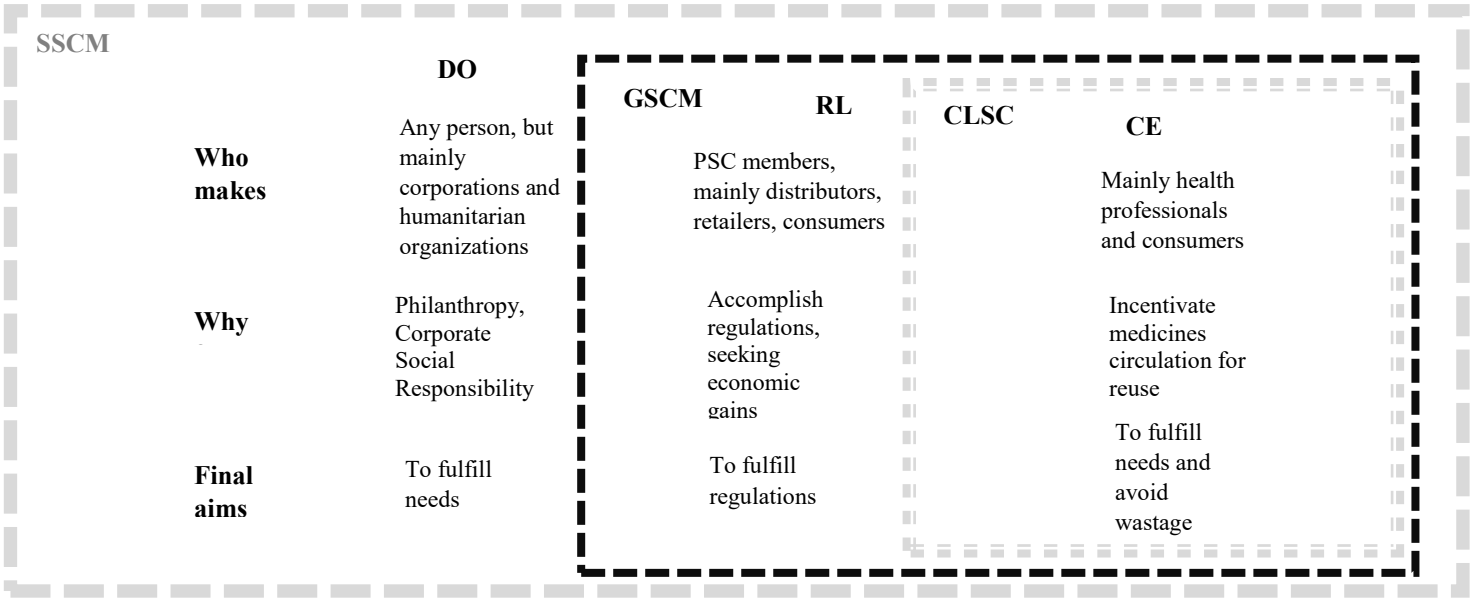
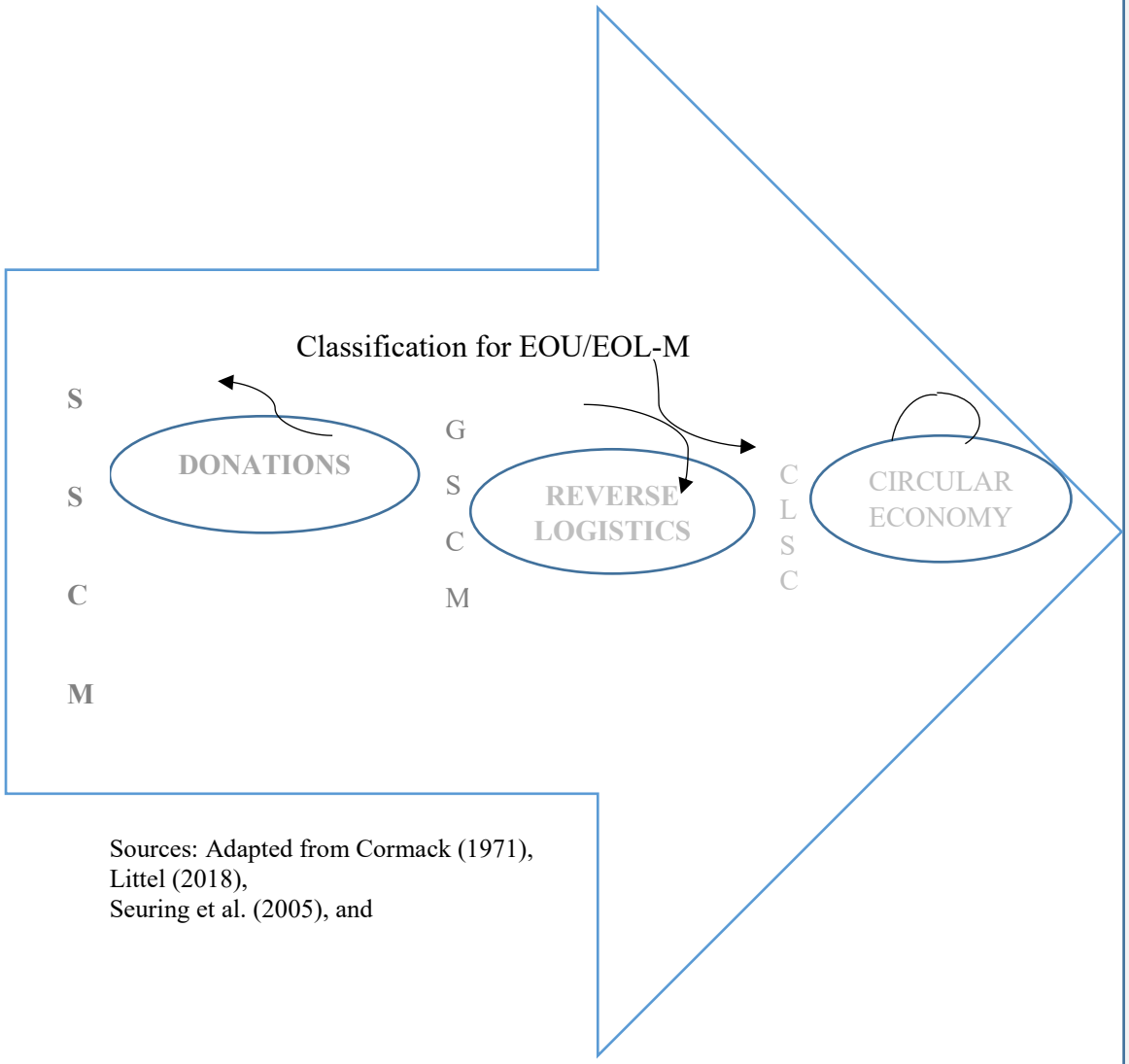
Figure 1 - Categories of medicines reverse flows and associated SCM concepts



SSCM – Sustainable Supply Chain Management; GSCM – Green Supply Chain Management; CLSC – Closed Loop Supply Chain; DO – Donations; RL – Reverse Logistics; CE – Circular Economy.

Figure 2 – Research Design for Qualitative Classificatory Review



Sources: Adapted from Cormack (1971), Littel (2018), Seuring et al. (2005), and

FOCUS – Reverse flows of EOU-EOL-M in PSC through classificatory review.
Categories of reverse flows: Donations (DO), Reverse Logistics (RL), and Circular Economy (CE).
GOALS - Answer the questions for each category:

(i) What are the elements of the forward PSC processes that impact PSC reverse flows? (Constraints)
(ii) In what stage of the PSC are the reverse flows identified?
(iii) What does the academic literature recommend for improving PSC reverse flows?
COVERAGE – Web of Science, Emerald, Wiley, Taylor & Francis, Science Direct (any time), Google Scholar (from 2014 on).

RESULTS

DESCRIPTIVE ANALYSIS

Number total of selected references published by year.
More representative countries in which the research is carried out for each category.
Number of references by disciplinary field of the selected studies.
Methodologies employed in the studies.
Journals of the publications by category (Appendices).

CLASSIFICATORY ANALYSIS – ANSWERS

DONATIONS – (i) Constraints (ii), where occurs (iii), recommendations for improvement.
RL – (i) Barriers, drivers/opportunities, [reviews, models, specific constraints*], (ii) where occurs, (iii) recommendations for improvement.
CE – [CE and CLSC, CE as epistemical view of social responsibility, CE upstream the chain (green chemical), CE downstream the chain (packaging and bioeconomy), reusing and wastage avoidance], (i) constraints, (ii) where occurs, (iii) recommendations for improvement.

*Emerging subjects (beyond questions)

Seuring and Müller (2008).

Figure 3 – Chronology of publications

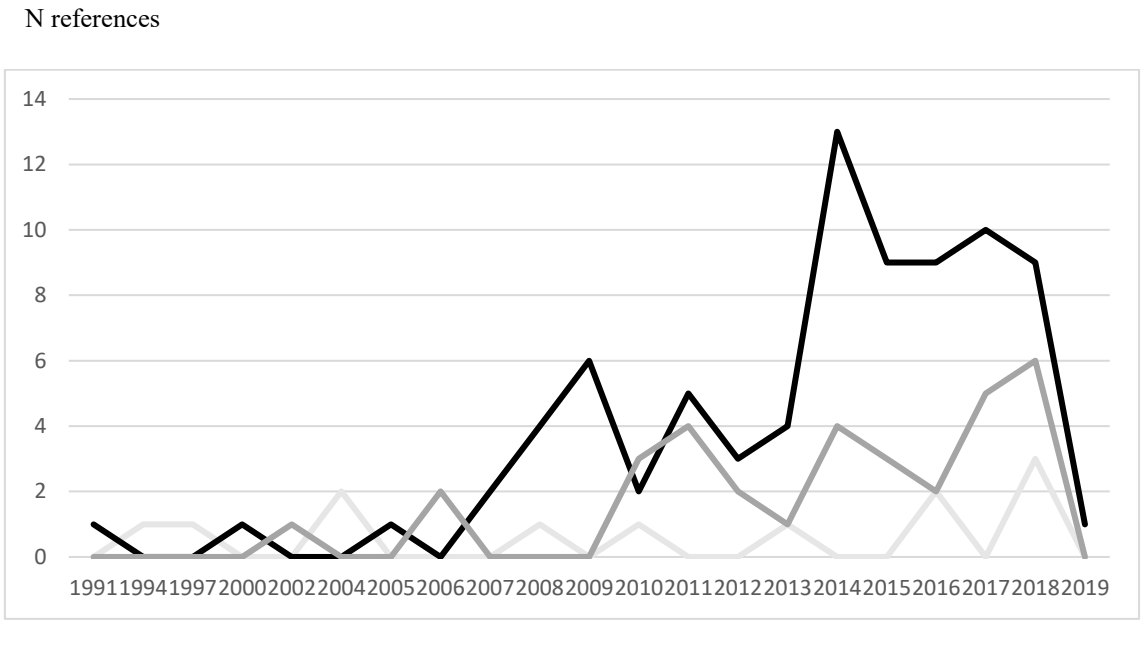
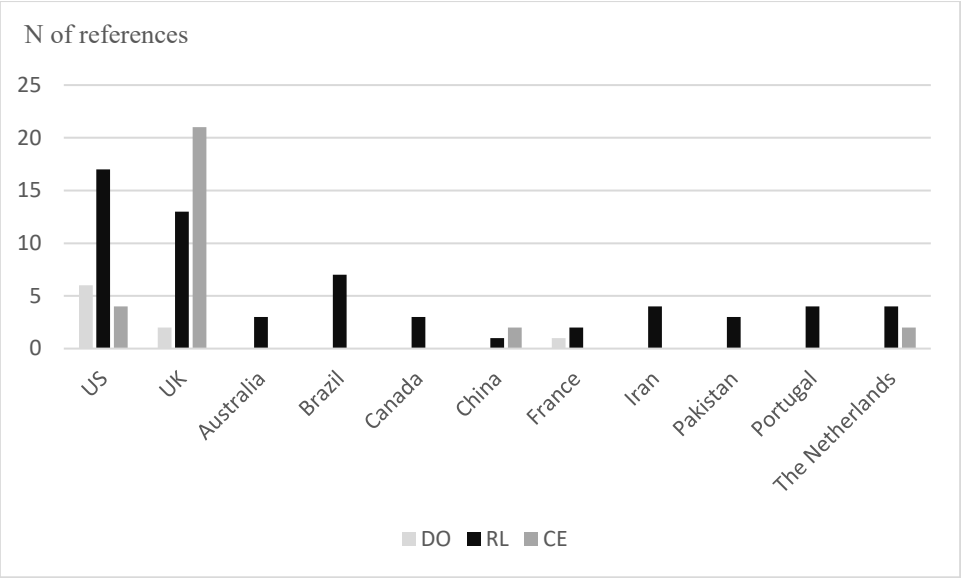
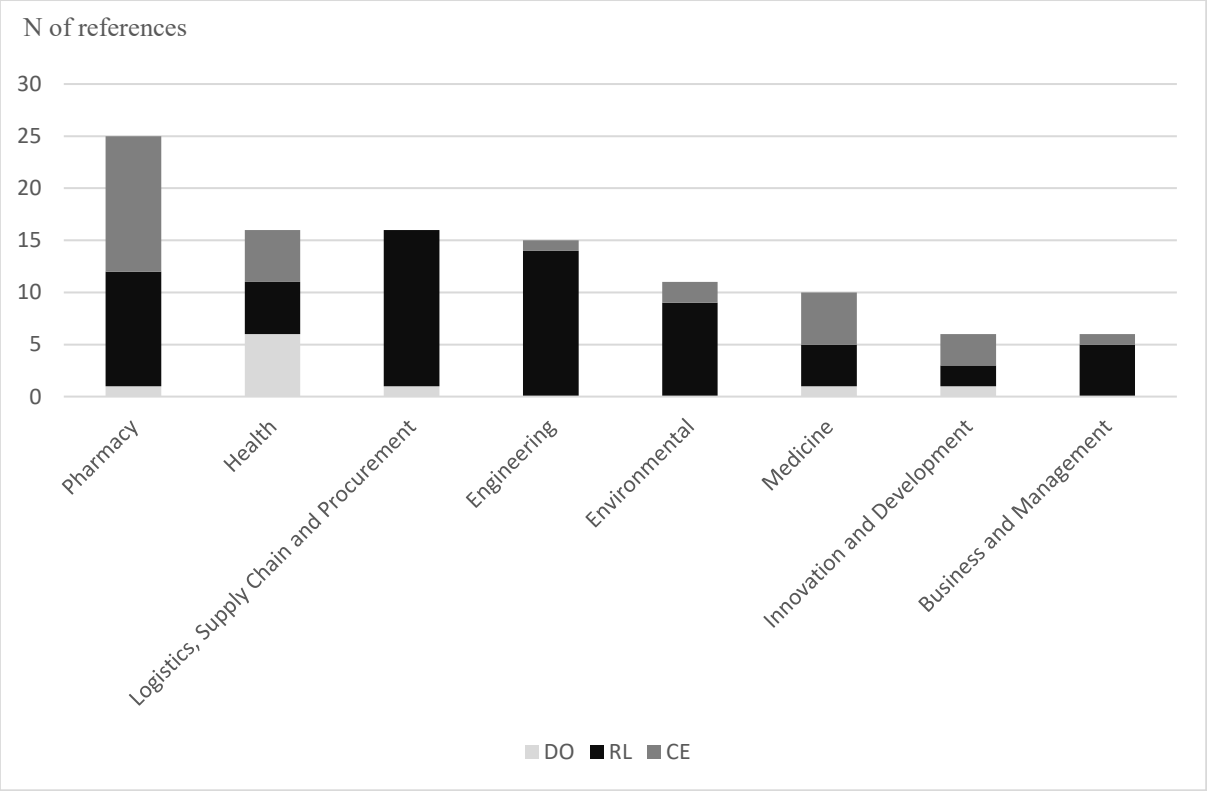


Figure 4 – Main countries in which medicines reverse flows research is carried out



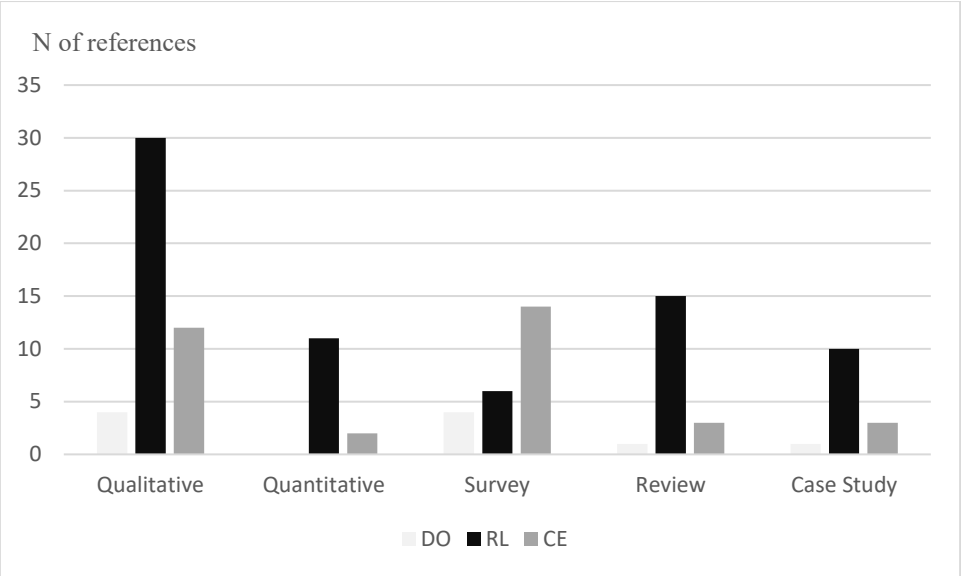
DO = donations; RL = Reverse Logistics; CE = Circular Economy
There were considered countries with at least 2 occurrencies in at least one of the categories

Figure 5 – Number of references by disciplinary fields of the selected publications



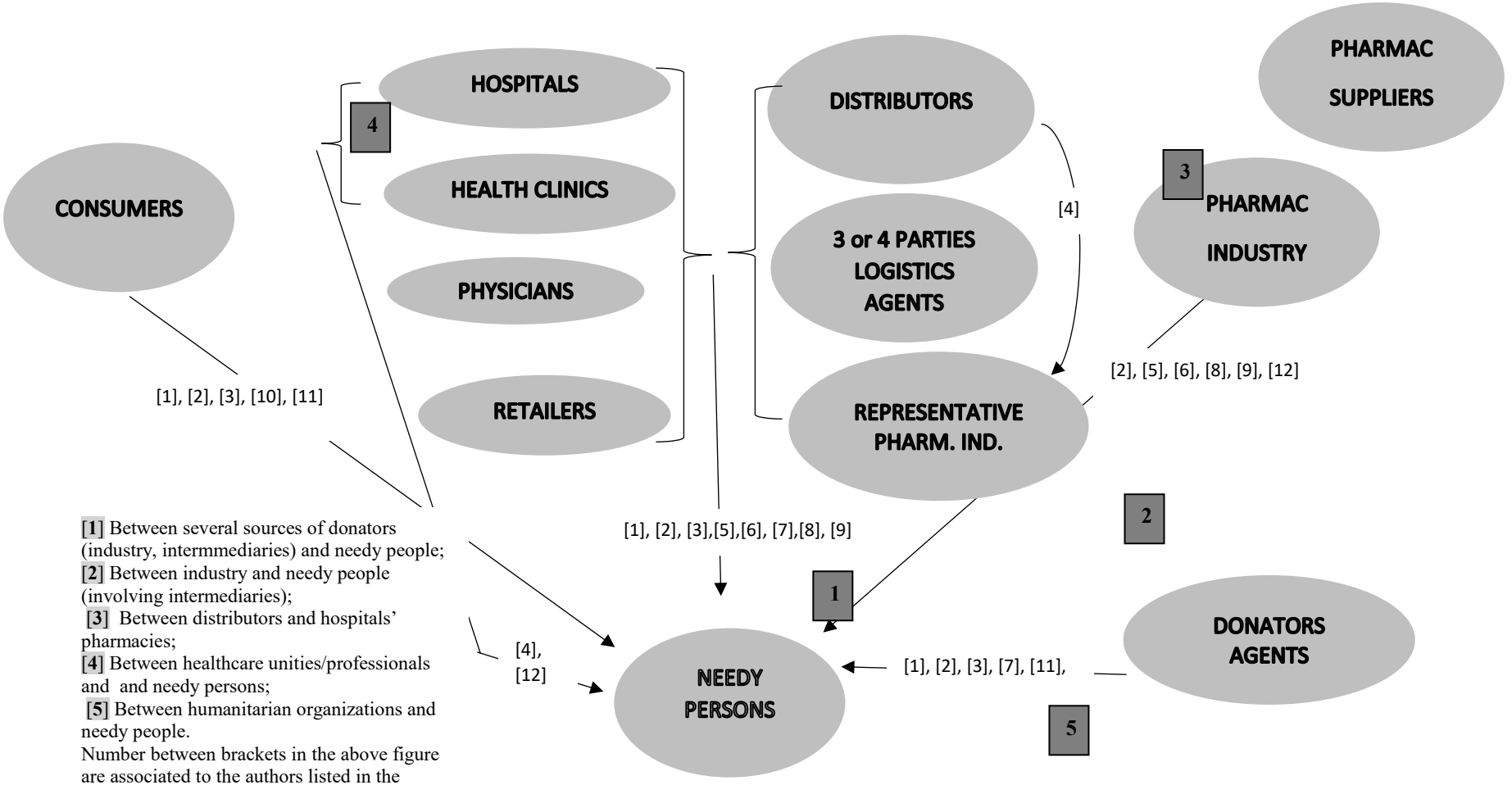
DO = donations; RL = Reverse Logistics; CE = Circular Economy

Figure 6 – Methodologies employed in the reviewed documents



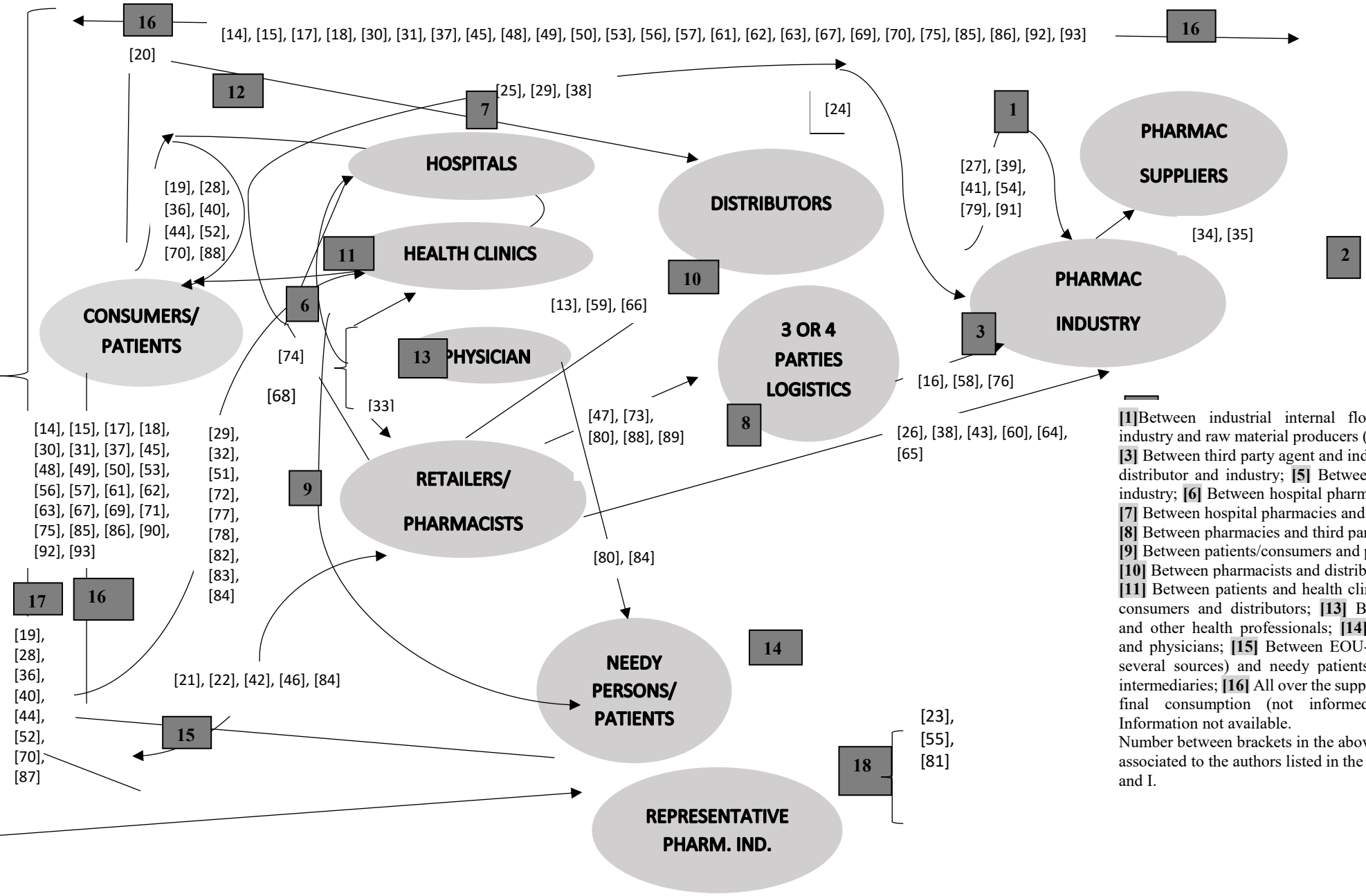
DO = donations; RL = Reverse Logistics; CE = Circular Economy

Figure 7 – Roots of Donations in reverse flows of the PSC



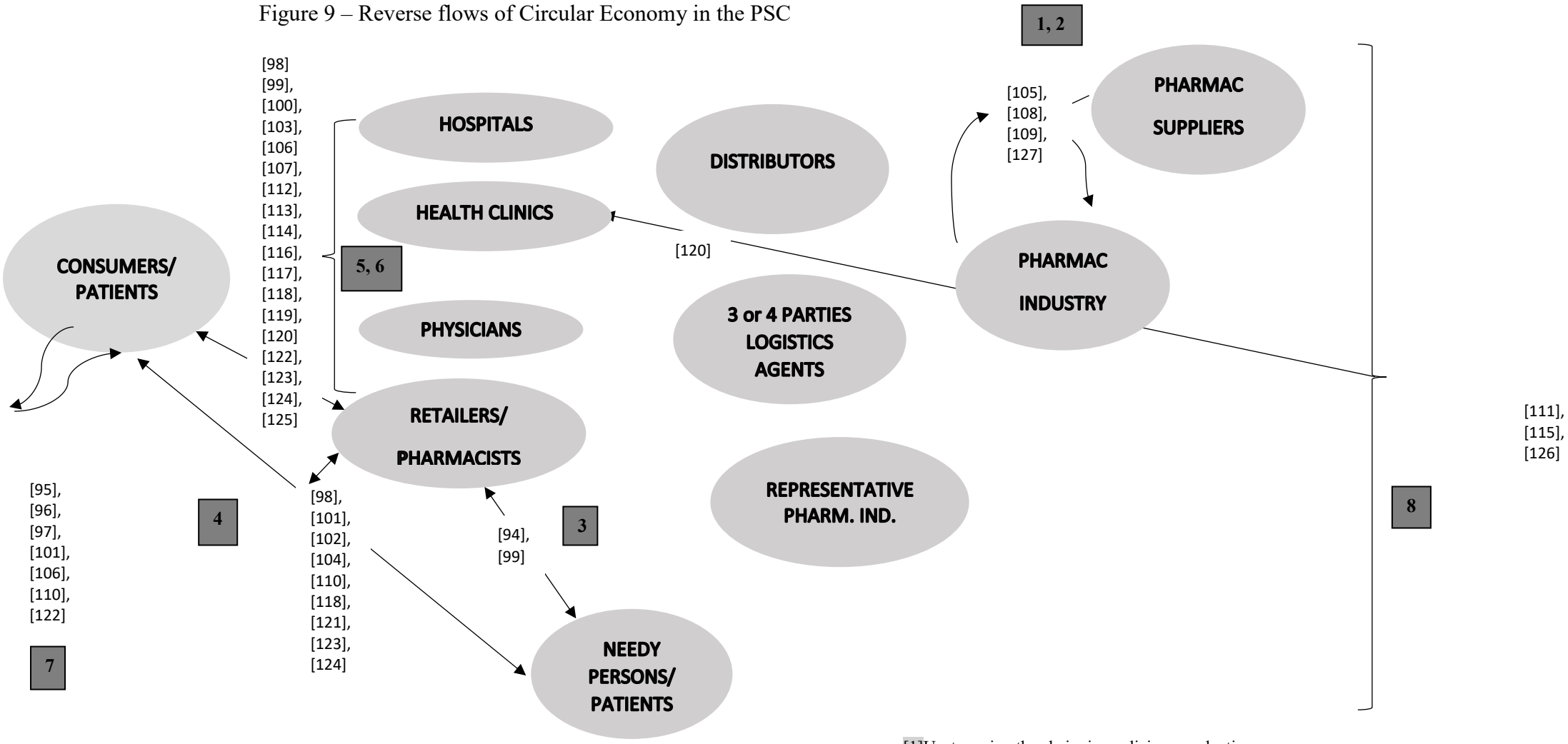
[1] Between several sources of donators (industry, intermmediaries) and needy people;
[2] Between industry and needy people (involving intermediaries);
[3] Between distributors and hospitals' pharmacies;
[4] Between healthcare unities/professionals and and needy persons;
[5] Between humanitarian organizations and needy people.
Number between brackets in the above figure are associated to the authors listed in the Appendices D, E, and F.

Figure 8 – Reverse Logistics flows in the PSC



[1]Between industrial internal flows; **[2]** Between industry and raw material producers (suppliers);
[3] Between third party agent and industry; **[4]** Between distributor and industry; **[5]** Between pharmacists and industry; **[6]** Between hospital pharmacies and patients;
[7] Between hospital pharmacies and industry;
[8] Between pharmacies and third party agents;
[9] Between patients/consumers and pharmacists;
[10] Between pharmacists and distributors;
[11] Between patients and health clinics; **[12]** Between consumers and distributors; **[13]** Between physicians and other health professionals; **[14]** Between patients and physicians; **[15]** Between EOU-M donators (from several sources) and needy patients, with or without intermediaries; **[16]** All over the supply chain; **[17]** After final consumption (not informed receiver); **[18]** Information not available.
Number between brackets in the above figure are associated to the authors listed in the Appendices G, H, and I.

Figure 9 – Reverse flows of Circular Economy in the PSC



[1]Upstreaming the chain, in medicines production;
[2]Between pharmaceutical industry and package supplier;
[3] Between patients and pharmacists;
[4] Between pharmacists, patients and needy people;
[5] Between patients, physicians or other health professionals (nurses);
[6] Between several sources of EOU-M donations and a health clinic;
[7] During or after the patients' consumption;
[8] All over the supply chain.
Number between brackets in the above figure are associated to the authors listed in the Appendices J, K, and L.

Table 1 - Results of the comprehensive literature review for EOU/EOL-M

Search strategy	**Key expressions**	**Web of Science**[1]		**Emerald**		**Wiley**		**Taylor & Francis**		**Science Direct**		**Google Scholar**		**Final Results**
		Any time		Any time		Any time		Any time		Any time		Since 2014		
		P[2]	F[2]	P	F	P	F	P	F	P	F			
First search	"pharmaceutical supply chain and drug(s)/ medicine(s) donation(s)"	127	**4**	35	**1**	119	**0**	53	**1**	548	**1**	304	**5**	**12**
Second search	"drug(s)/medicine (s) donation(s) and 'reverse logistics'"	87	**20**	28	**12**	18	**3**	30	**1**	24	**22**	578	**23**	**81**
Third search	"drug(s)/medicine (s) donation(s)" and "circular economy" and "medicines wastage"	27	**14**	63	**0**	32	**7**	0	**0**	72	**3**	477	**10**	**34**
Total		241	**38**	126	**13**	169	**10**	83	**2**	644	**26**	1,359	**38**	**127**

[1]The search in Web of Science (WoS) was limited to CAB Abstracts/Global Health, Medline and PubMed. Other meta-bases of WoS, as Inspec (for engineering and technological issues), Food Science Technology Abstracts, Patent and Data Collections, Regional Hosted Collection, Specialty Collections (Current Contents, BIOSIS Citation, BIOSIS Preview, Biological Abstracts and Zoological Records), were not included.

[2] Previous (P) and Filtered (F) results, after Titles and Abstracts reading and after elimination of repeated results.

Table 2 – N of publications by year for each category

Year	DO	RL	CE
1991	1	1	0
1994	1	0	0
2000	0	1	0
2002	0	0	1
2004	2	0	0
2005	0	1	1
2006	0	0	2
2007	0	2	0
2008	1	4	0
2009	0	6	0
2010	1	2	3
2011	0	5	4
2012	0	3	2
2013	1	4	1
2014	0	13	4
2015	0	9	3
2016	2	9	2
2017	0	11	5
2018	3	9	6
2019	0	1	0

DO – Donations; RL – Reverse Logistics; CE – Circular Economy

Table 3 - Main countries in which the research on medicines reverse flows is carried out

Country	DO	RL	CE	Total
US	6	17	4	27
UK	2	13	21	36
Australia	0	3	0	3
Brazil	0	7	0	7
Canada	0	3	0	3
China	0	1	2	3
France	1	2	0	3
Iran	0	4	0	4
Pakistan	0	3	0	3
Portugal	0	4	0	4
The Netherlands	0	4	2	6

DO = donations; RL = Reverse Logistics; CE = Circular Economy
There were considered countries with at least 2 occurrencies in at least one of the categories

Table 4 – Main fields in which research on reverse flows of medicines was identified

Field	DO	RL	CE	Total
Pharmacy	1	11	13	25
Health	6	5	5	16
Logistics, Supply Chain and Procurement	1	15	0	16
Engineering	0	14	1	15
Environmental	0	9	2	11
Medicine	1	4	5	10
Innovation and Development	1	2	3	6
Business and Management	0	5	1	6
Other (not identified)	2	16	4	22

DO – Donations; RL – Reverse Logistics; CE – Circular Economy

Table 5 – Methodologies employed in the reviewed documents

Methodology	DO	RL	CE	Total
Qualitative	4	30	12	46
Quantitative	0	11	2	13
Survey	4	6	14	34
Review	1	15	3	20
Case Study	1	10	3	14

DO – Donations; RL – Reverse Logistics; CE – Circular Economy

Appendix A – Donations - Authorship by country and source of publication

Authorship	Country	Source/Journal
Attaran (2004)	UK	Health Affairs
Beckmans et al. (1997)	Belgium	The New England Journal of Medicine
Bero et al. (2010)	US	Bulletin of the WHO
Chukwu et al. (2016)	Nigeria	Research in Social and Administrative Pharmacy
Colatrella (2008)	US	Annals of the Tropical Med. & Parasitology
Collins (2004)	US	Perspectives in Biology and Medicine
Dolinskaya et al. (2018)	US, Germany	Jounal of Humanitarian Logistics and Supply Chain Management
Guilbaud (2018)	France	Journal of International Political Theory
Jenny et al. (2016)	US	Globalization and Health
Kale et al. (2013)	UK	Innovation and Development
Nicoli et al. (2018)	Italy	Int. Health
Smego and Gebrian(1994)	US	Clinical Infectious Diseases

Appendix B – Reverse Logistics - Authorship by country and source of publication

REVERSE LOGISTICS		
Authorship	**Country**	**Journal/Source**
Abbas and Faroquie (2018)	Oman, India	International Journal of Logistics Economics and Globalisation
Abidi et al. (2015)	The Netherlands, UK, Germany	Journal of Humanitarian Logistics and Supply Chain Management
Aghalaya et al. (2012)	India, New Zealand	Australian and New Zealand Academy of Management Conference. Proceedings
Ali (2015)	Norway	Doct. Dissertation
Amaro and Barbosa-Povoa (2008)	Portugal	Computers and Chemical Engineering
Amaro and Barbosa-Povoa (2009)	Portugal	Computers and Chemical Engineering
Balbino and Balbino (2011)	Brazil	Âmbito Jurídico [Legal Field]
Baxerres and Hesran (2011)	France	Social Science and Medicine
Bekker et al. (2018)	The Netherlands	Int. J. Clin. Pharm
Blackstone et al. (2014)	US	Am. Health Drug Benefits
Bolineni (2016)	US	Doct. Dissertation
Bueno et al. (2017)	Brazil	South American Development Society Journal
Bravo and Carvalho (2015)	Portugal	Int.J. Procurement Management
Breen and Xie (2015)	UK	Int. J.Procurement Management
Cameron et al. (2009)	Switzerland	The Lancet
Campos et al. (2017)	Brazil	Supply Chain Management: An International Journal
Chao et al. (2007)	Taiwan	Technovation
De Brito et al. (2005)	The Netherlands	Book chapter (Springer)
Ding (2018)	UK	Process Safety and Environmental Protection
El-Hamamsy et al. (2011)	Egypt	International Journal of Pharmaceutical Studies and Research
Elliot (2013)	UK	The Journal of Global Business Issues
Enyinda and Szmerekovsky (2008)	Arabian Emirates, US	Prescriber. The Journal of Prescribing and Medicines Management
Enyinda and Tolliver (2009)	Arabian Emirates , US	Journal of African Business
Falqueto and Kligerman (2013)	Brazil	Ciência & Saúde Coletiva [Science & Collective Health]
Foster (1991)	UK	Soc. Sci. Med.
Franco and Alfonso-Lizarazo (2017)	Colombia, France	Hindawi Complexity
Halabi and Gostin (2015)	US	Book chapter, Academic Press
He et al.(2016)	China	Procedia Environmental Sciences
Imran et al. (2018)	South Korea, Pakistan	Journal of Manufacturing Systems
Kagashe et al. (2014)	Tanzania	. Journal of Applied Pharmaceutical Science
Kamba et al. (2017)	Uganda	Bulletin World Health Organ
Kelly et al. (2018)	Australia, New Zealand	BMC Public Health
Khan and Subzwari (2009)	Pakistan	South Asian Journal of Management Sciences
Kifli et al. (2018)	Brunei	Asian Journal of Pharmaceutical and Clinical Research
Kongar et al. (2015)	US, Turkey	Information Technology & Management
Kraiselburd and Ydav (2013)	Costa Rica, US	Production and Operations Management
Kumar et al. (2009)	US	Int. Journal of Productivity and Performance Management
Kumar and Saravanan (2016)	India	World Journal of Pharmacy and Pharmaceutical Sciences
Kwateng et al. (2014)	Ghana	Global Journal of Business Research
Law et al. (2014)	US	Research in Social and Administrative Pharmacy
Lima et al. (2018)	Brazil	Supply Chain Management: An International Journal
Li and Hamblin (2016)	UK	Journal of Cleaner Production
Lücker and Seifert (2017)	Switzerland	Omega
Mackey et al. (2017)	US	Expert Opinion on Drug and Safety
Masoumi and Nagournay (2012)	US	Transportation Research E
Moslemi et al. (2017)	Iran, Turkey, US	Int.J. Syst. Assur. Eng. Manag.

Mustafa and Potter (2009)	UK	Supply Chain Management: An International Journal
Nakyanzi et al. (2010)	Uganda	Bulletin of The World Health Organization
Narayana et al. (2014 a)	India	The International Journal of Logistics Management
Narayana et al. (2014 b)	India	Journal of Purchasing & Supply Management
Narayana et al. (2019)	India	Journal of Cleaner Production
Nematollahi et al. (2017a)	Iran	Journal of Cleaner Production
Nematollahi et al. (2017b)	Iran	Int. J.Production Economics
Nematollahi et al. (2018)	Iran, UK, Malaysia, Singapore	Journal of Cleaner Production
Niza et al. (2014)	Portugal	Journal of Cleaner Production
Papalexi et al. (2014)	UK	Annual Conference Special Issue for the Logistics Research Network (LRN), Wyley
Pereira et al. (2017)	Brazil	Environ.Sci.Pollut. Res.
Pinto et al. et al. (2014)	Brazil	Eng. Sanit. Ambient.
Pribluda et al. (2014)	US	Pharmaceutical Regulatory Affairs
Ritchie et al. (2000)	UK	Supply Chain Management: An International Journal
Rolevick-Kalińska (2016)	Poland	Transportation Research Procedia
Romero (2013)	Canada	Proceedings of the World Congress on Engineering and Computer Science, Vol II
Rossetti et al. (2011)	US	International Journal of Physical Distribution & Logistics Management
Sanderson et al. (2015)	UK	Health Services and Delivery Research
Saravanan and Kumar (2016)	India	Indian Journal of Research in Pharmacy and Biotechnology
Serrou et al. (2014)	Morroco	Journal of Scientific & Engineering Research
Schiel (2018)	US	BrighamYoung University Law Review
Singh et al. (2016)	India	International Journal of Pharmaceutical and Healthcare Marketing
Subzwari and Nasir (2015)	Pakistan	South Asian Journal of Management Sciences
Thepsatidsilph (2015)	Australia	Doct. Thesis
Tong et al. (2011)	New Zealand	Environment International
Trueman et al. (2010)	UK	Report, YHEC/School of Pharmacy, University of London
Tzeng et al. (2008)	Taiwan	Int. J. Production Economics
Urias (2017)	The Netherlands	Book chapter, Emerald Insight
Vogler et al. (2014)	Austria	Journal of Pharmaceutical Policy and Practice
Weraikat et al. (2016 a)	Canada	Int. J. Productions Economics
Weraikat et al. (2016 b)	Canada	Computers & Industrial Engineering
Wyld and Jones (2007)	US	. Int. J. Integrated Supply Management
Xie and Breen (2012)	UK	Supply Chain Management: An International Journal
Xie and Breen (2014)	UK	Supply Chain Management: An International Journal
Ziance (2008)	US	Journal of the American Pharmacian Association

Appendix C – Circular Economy - Authorship by country and source of publication

Authorship	Country	Journal/Source
Alhamad et al. (2018)	UK	International Journal of Pharmacy Practice
AlSamanhodi et al. (2017)	Saudi Arabia	Tropical Journal of Pharmaceutical Research
Andrews et al. (2010)	UK, US, Ireland, Belgium	Organic Process Research & Development
Bange and Morgan (2018)	UK	Geriatric Medicine Care
Bekker et al. (2017)	The Netherlands	Int. J. Clin. Pharm.
Connelly (2018)	UK	The Pharmaceutical Journal. A Royal Pharmaceutical Society Publication
Daniszewsi et al. (2002)	UK	International Journal of Pharmacy Practice
De Filippis et al. (2012)	UK	WIT Transactions on Ecology and the Environment
Gyanendra et al. (2011)	India	International Research Journal of Pharmacy
Hampson and Ottey (2015)	UK	Prescriber
Jesson et al. (2005)	UK	Primary Health Care Research and Development
Jimenez-Gonzalez et al. (2011)	US	Organic Process Research & Development
Kane et al. (2018)	The Netherlands	Resources Conservation and Recycling
King et al. (2018)	UK, Germany	British Journal of General Practice
Koenig et al. (2018)	US, UK	Organic Process Research & Development
Latif et al. (2013)	UK	Administrative Pharmacy
Lorenzini et al. (2017)	Sweden	Journal of Business Research
McRae et al. (2016)	UK	Int.J.Pharm. Practice
Mwencha et al. (2017)	Tanzania, US	Global Health: Science and Practice
O'Leary et al. (2006)	UK	Int.J.Pharm. Practice
Petty et al. (2014)	UK	BMC Health Services Research
Shah et al. (2014)	UK	Journal of Community Nursing
Søndergaard (2006)	Denmark	Value in Health
Taitel et al. (2012)	US	Medicare and Medicaid Research Review
Taylor (2010)	UK	The Pharmaceutical Journal
Taylor (2014)	UK	Prescriber
Toh and Chew (2016)	Singapore	Palliative Medicine
Twigg et al. (2015)	UK	International Journal of Pharmacy Practice
West et al. (2014)	UK	Int. J. Clin. Pharm
West et al. (2015)	UK, Malta	Eur. J. Hosp. Pharm
White et al. (2010)	UK	International Journal of Pharmacy Practice
Ze-hua et al. (2011)	China	Energy Procedia
Zhang (2017)	China	Chemical Engineering Transactions

Appendix D – Barriers in the forward PSC that impact EOU-M Donations

Identified constraints of the forward PSC processes that impact PSC reverse flows **Sources**	Excessive amounts of production; demand uncertainties; quality of products	Inappropriate types and amounts of donations	Package/ labelling, transportation, storage problems	Treatment/ prescription changes	Information not available or unclear
[1] Attaran (2004)	X				
[2] Beckmans et al. (1997)	X	X	X		
[3] Bero et al. (2010)	X	X	X		
[4] Chukwu wt al. (2016)					X
[5] Colatrella (2008)			X		X
[6] Collins (2004)	X				
[7] Dolinskaya et al. (2018)	X		X		
[8] Guilbaud (2018)					X
[9] Jenny et al. (2016)		X		X	
[10] Kale et al. (2013)				X	X
[11] Nicoli et al. (2018)		X			X
[12] Smego and Gebrian(1994)					X

Appendix E – Where EOU-M Donations takes place in PSC

Stage of the PSC is the reverse flow identified **Sources**	[1]	[2]	[3]	[4]	[5]
[1] Attaran (2004)	X				
[2] Beckmans et al. (1997)	X				
[3] Bero et al. (2010)	X				
[4] Chukwu et al. (2016)			X		
[5] Colatrella (2008)		X			
[6] Collins (2004)		X			
[7] Dolinskaya et al. (2018)					X
[8] Guilbaud (2018)		X			
[9] Jenny et al. (2016)		X			
[10] Kale et al. (2010)	X				
[11] Nicoli et al. (2018)	X				
[12] Smego and Gebrian (1994)				X	

[1] Between several sources of donators (industry, intermmediaries) and needy people; [2] Between industry and needy people (involving intermediaries); [3] Between distributors and hospitals' pharmacies; [4] Between healthcare unities/professionals and and needy persons; [5] Between humanitarian organizations and needy people.

Appendix F – Recommendations of EOU-M Donations studies for improving PSC reverse flows

What the reviewed studies recommend for improving PSC reverse flows? **Sources**	Improving collaboration between stakeholders (including access of medicines to vulnerable persons)	Improving transportation, storage, overall management of EOU-EOL-M	Improving adherence to best practice donations; investigating need and feasibility of donations	Reducing demand uncertainties	Developing frameworks for donations impact assessment	Improving guidance or capacity of health professionals
[1] Attaran (2004)			X			
[2] Beckmans et al. (1997)	X	X				
[3] Bero et al. (2010)			X			
[4] Chukwu et al. (2016)			X			X
[5] Colatrella (2008)	X					
[6] Collins (2004)			X			
[7] Dolinskaya et al. (2018)	X			X		
[8] Guilbaud (2018)	X					
[9] Jenny et al. (2016)					X	
[11] Nicoli et al. (2018)					X	
[12] Smego and Gebrian (1994)			X			

Appendix G - Barriers in the forward PSC that impact EOU/EOL-M RL

Identified constraints of the forward PSC processes that impact PSC reverse flows (see caption below) **Sources**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
[13] Abbas and Faroquie (2018)	X			X																				
[14] Abidi et al. (2015)	X																							
[15]Aghalaya et al. (2012)				X	X																			
[16] Ali (2015)			X																		X			
[17] Amaro and Barbosa-Povoa (2008)		X		X	X													X						
[18] Amaro and Barbosa-Povoa (2009)		X		X																				
[19] Balbino and Balbino (2011)					X																			
[20] Baxerres and Hesran (2011)			X									X					X							
[21] Bekker et al. (2018)				X																	X			
[22] Blackstone et al. (2014)	X																							
[23] Bolineni (2016)											X	X	X											
[24] Bueno et al. (2017)					X																			
[25] Bravo and Carvalho (2015)			X	X																				
[26] Breen and Xie (2015)		X		X																				
[27] Cameron et al. (2009)						X												X						
[28] Campos et al. (2017)														X										
[29] Chao et al. (2007)																	X				X			
[30] De Brito et al. (2005)	X																							
[31] Ding (2018)	X										X			X		X							X	
[32] El-Hamamsy et al. (2011)																								
[33] Elliot (2013)																						X		X
[34] Enyinda and Szmerekovsky (2008)																	X					X		
[35] Enyinda and Tolliver (2009)														X			X	X		X		X		X

[36] Falqueto and Kligerman (2013)					X												X							
[37] Foster (1991)							X								X									
[38] Franco and Alfonso-Lizarazo (2017)												X												
[39] Halabi and Gostin (2015)	X																							
[40] He et al. (2016)					X																			
[41] Imran et al. (2018)			X																					
[42] Kagashe et al. (2014)																								X
[43] Kamba et al. (2017)				X																				
[44] Kelly et al. (2018)																								X
[45] Khan and Subzwari (2009)											X			X			X	X						
[46] Kifli et al. (2018)				X																				
[47] Kongar et al. (2015)															X						X			
[48] Kraiselburd and Ydav (2013)	X											X												
[49] Kumar et al. (2009)									X															
[50] Kumar and Saravanan (2016)																					X			
[51] Kwateng et al. (2014)	X							X				X												
[52] Law et al. (2014)																				X				
[53] Lima et al. (2018)	X	X												X										
[54] Li and Hamblin (2016)			X																X					
[55] Lücker and Seifert (2017)		X		X																				
[56] Masoumi and Nagournay (2012)	X				X																			
[57] Mackey and Nayyar (2017)	X								X			X												
[58] Moslemi et al. (2017)															X						X			
[59] Mustafa and Potter (2009)				X																				
[60] Nakyanzi et al. (2010)															X						X			
[61] Narayana et al. (2014 a)					X																			
[62] Narayana et al. (2014 b)		X	X																					
[63] Narayana et al. (2019)				X							X				X						X			
[64] Nematollahi et al. (2017a)				X																				

[65] Nematollahi et al. (2017b)				X																			
[66] Nematollahi et al. (2018)				X																			
[67] Niza et al. (2014)													X		X								
[68] Papalexi et al. (2014)					X																		
[69] Pereira et al. (2017)																							X
[70] Pinto et al. et al. (2014)					X																		
[71] Pribluda et al. (2014)			X																				
[72] Ritchie et al. (2000)							X																
[73] Rolevick-Kalińska (2016)																							
[74] Romero (2013)									X				X										
[75] Rossetti et al. (2011)										X				X									
[76] Sanderson et al. (2015)			X				X																
[77]Saravanan and Kumar					X																		
[78] Schiel (2018)										X								X	X				
[79] Serrou et al. (2014)								X															
[80] Singh et al. (2016)	X																						
[81] Subzwari and Nasir (2015)																	X	X			X		
[82] Thepsatidsilph (2015)																		X					
[83] Tong et al. (2011)																						X	
[84] Trueman et al. (2010)																					X		X
[85] Tzeng et al. (2008)				X																			
[86] Urias (2017)						X												X					
[87] Vogler et al. (2014)																							X
[88] Weraikat et al. (2016 a)				X																X			
[89] Weraikat et al. (2016 b)	X												X										
[90] Wyld and Jones (2007)			X																			X	
[91] Xie and Breen (2012)																						X	X
[92] Xie and Breen (2014)																							
[93] Ziance (2008)	X																						

Planning/operational constraints: (1) Extension of the supply chain/difficulties for coordination between stakeholders; (2) Difficulties for flows management/lack of flexibility; (3) Quality control problems (including package); (4) Inventory/ production planning problems; (5) Excessive

production; (6) Lack of specific medicines availability; (7) Procurement problems; (8) Storage problems; (9) Delivery delays; (10) Logistics inefficiency;
(11) High perishability/low shelf life of medicines. **Costs/prices constraints**: (12) High costs of operation;
(13) High costs of distribution; (14) High costs of transportation; (15) High prices for consumers.
Public policies constraints: (16) Lack of transparency in prices; (17) Lack of regulatory frames;
(18) Defective intellectual protection; (19) Informal trade/counterfeiting. **Cultural constraints**:
(20) Lack of consumers' awareness; (21) Lack of innovation culture;
(22) Lack of information/transparency between physicians and patients or presciption problems;
(23) Lack of training/capacity building of health professionals; (24) Patient behaviour problems
(non adherence to medicines, treatment abandonment, careless attitudes).
All blanket spaces for a source means "information not available on this subject".

Appendix H - Where EOU/EOL-M RL takes place in PSC

Stage of the PSC is the reverse flow identified (see caption below) **Sources**	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]
[13] Abbas and Faroquie (2018)										X								
[14] Abidi et al. (2015)																X		
[15]Aghalaya et al. (2012)																X		
[16] Ali (2015)			X															
[17] Amaro and Barbosa-Povoa (2008)																X		
[18] Amaro and Barbosa-Povoa (2009)																X		
[19] Balbino and Balbino (2011)																	X	
[20] Baxerres and Hesran (2011)												X						
[21] Bekker et al. (2018)															X			
[22] Blackstone et al. (2014)															X			
[23] Bolineni (2016)																		X
[24] Bueno et al. (2017)									X									
[25] Bravo and Carvalho (2015)							X											
[26] Breen and Xie (2015)					X													
[27] Cameron et al. (2009)	X																	
[28] Campos et al. (2017)																	X	
[29] Chao et al. (2007)							X				X							
[30] De Brito et al. (2005)																X		
[31] Ding (2018)																X		
[32] El-Hamamsy et al. (2011)									X									
[33] Elliot (2013)													X					
[34] Enyinda and Szmerekovsky (2008)		X																
[35] Enyinda and Tolliver (2009)		X																

[36] Falqueto and Kligerman (2013)																	X	
[37] Foster (1991)																X		
[38] Franco and Alfonso-Lizarazo					X		X											
[39] Halabi and Gostin (2015)	X																	
[40] He et al. (2016)																	X	
[41] Imran et al. (2018)	X																	
[42] Kagashe et al. (2014)															X			
[43] Kamba et al. (2017)					X													
[44] Kelly et al. (2018)																	X	
[45] Khan and Subzwari (2009)																X		
[46] Kifli et al. (2018)															X			
[47] Kongar et al. (2015)								X										
[48] Kraiselburd and Ydav (2013)																X		
[49] Kumar et al. (2009)																X		
[50] Kumar and Saravanan (2016)																X		
[51] Kwateng et al. (2014)									X									
[52] Law et al. (2014)																	X	
[53] Lima et al. (2018)																X		
[54] Li and Hamblin (2016)	X																	
[55] Lücker and Seifert (2017)																		X
[56] Masoumi and Nagournay (2012)																X		
[57] Mackey and Nayyar (2017)																X		
[58] Moslemi et al. (2017)			X															
[59] Mustafa and Potter (2009)										X								
[60] Nakyanzi et al. (2010)					X													
[61] Narayana et al. (2014 a)																X		

[62] Narayana et al. (2014 b)																X		
[63] Narayana et al. (2019)																X		
[64] Nematollahi et al. (2017a)					X													
[65] Nematollahi et al. (2017b)					X													
[66] Nematollahi et al. (2018)										X								
[67] Niza et al. (2014)																X		
[68] Papalexi et al. (2014)									X									
[69] Pereira et al. (2017)																X		
[70] Pinto et al. et al. (2014)																	X	
[71] Pribluda et al. (2014)																X		
[72] Ritchie et al. (2000)									X									
[73] Rolevick-Kalińska (2016)								X										
[74] Romero (2013)						X												
[75] Rossetti et al. (2011)																X		
[76] Sanderson et al. (2015)			X															
[77] Saravanan and Kumar (2016)									X									
[78] Schiel (2018)									X									
[79] Serrou et al. (2014)	X																	
[80] Singh et al. (2016)								X						X				
[81] Subzwari and Nasir (2015)																		X
[82] Thepsatidsilp h (2015)									X									
[83] Tong et al. (2011)									X									
[84] Trueman et al. (2010)									X					X	X			
[85] Tzeng et al. (2008)																X		
[86] Urias (2017)																X		
[87] Vogler et al. (2014)																	X	
[88] Weraikat et al. (2016 a)								X										
[89] Weraikat et al. (2016 b)								X										

[90] Wyld and Jones (2007)																X		
[91] Xie and Breen (2012)	X																	
[92] Xie and Breen (2014)																X		
[93] Ziance (2008)																X		

[1]Between industrial internal flows; [2] Between industry and raw material producers (suppliers); [3] Between third party agent and industry; [4] Between distributor and industry;[5] Between pharmacists and industry; [6] Between hospital pharmacies and patients; [7] Between hospital pharmacies and industry; [8] Between pharmacies and third party agents; [9] Between patients/consumers and pharmacists; [10] Between pharmacists and distributors; [11] Between patients and health clinics; [12] Between consumers and distributors;[13] Between physicians and other health professionals; [14] Between patients and physicians; [15] Between EOU-M donators (from several sources) and needy patients, with or without intermediaries; [16] All over the supply chain; [17] After final consumption (not informed receiver); [18] Information not available.

Appendix I - Recommendations of EOU/EOL-M RL studies for improving PSC RL

What the reviewed studies recommend for improving PSC RL? (see caption below) **Sources**	1	2	3	4	5	6	7	8	9	10	11	12	13
[13] Abbas and Faroquie (2018)													X
[14] Abidi et al. (2015)		X											
[15]Aghalaya et al. (2012)			X										
[16] Ali (2015)							X						
[17] Amaro and Barbosa-Povoa (2008)			X										
[18] Amaro and Barbosa-Povoa (2009)			X										
[19] Balbino and Balbino (2011)							X						X
[20] Baxerres and Hesran (2011)	X								X		X		
[21] Bekker et al. (2018)						X							X
[22] Blackstone et al. (2014)				X									
[23] Bolineni (2016)					X								
[24] Bueno et al. (2017)		X	X										
[25] Bravo and Carvalho (2015)	X												
[26] Breen and Xie (2015)						X							
[27] Cameron et al. (2009)													
[28] Campos et al. (2017)													X
[29] Chao et al. (2007)		X											
[30] De Brito et al. (2005)				X									
[31] Ding (2018)										X			
[32] El-Hamamsy et al. (2011)												X	
[33] Elliot (2013)				X									
[34] Enyinda and Szmerekovsky (2008)		X											
[35] Enyinda and Tolliver (2009)							X						X
[36] Falqueto and Kligerman (2013)		X						X					

[37] Foster (1991)							X						
[38] Franco and Alfonso-Lizarazo (2017)			X										
[39] Halabi and Gostin (2015)					X		X						
[40] He et al. (2016)			X										
[41] Imran et al. (2018)		X											
[42] Kagashe et al. (2014)					X					X			
[43] Kamba et al. (2017)							X	X					
[44] Kelly et al. (2018)							X						
[45] Khan and Subzwari (2009)										X			X
[46] Kifli et al. (2018)				X									
[47] Kongar et al. (2015)				X									
[48] Kraiselburd and Ydav (2013)									X				
[49] Kumar et al. (2009)													X
[50] Kumar and Saravanan (2016)			X										
[51] Kwateng et al. (2014)										X			X
[52] Law et al. (2014)		X		X	X								
[53] Lima et al. (2018)						X							
[54] Li and Hamblin (2016)	X	X											
[55] Lücker and Seifert (2017)					X								
[56] Masoumi and Nagournay (2012)			X										
[57] Mackey and Nayyar (2017)		X		X									
[58] Moslemi et al. (2017)	X	X											
[59] Mustafa and Potter (2009)											X		
[60] Nakyanzi et al. (2010)													X
[61] Narayana et al. (2014 a)	X												X
[62] Narayana et al. (2014 b)									X				X
[63] Narayana et al. (2019)		X	X										
[64] Nematollahi et al. (2017a)		X	X										
[65] Nematollahi et al. (2017b)			X										

[66] Nematollahi et al. (2018)							X						
[67] Niza et al. (2014)	X				X								
[68] Papalexi et al. (2014)						X							
[69] Pereira et al. (2017)						X							
[70] Pinto et al. et al. (2014)	X												
[71] Pribluda et al. (2014)										X			
[72] Ritchie et al. (2000)						X	X						
[73] Rolevick-Kalińska (2016)	X												
[74] Romero (2013)		X											
[75] Rossetti et al. (2011)											X		
[76] Sanderson et al. (2015)										X			
[77]Saravanan and Kumar (2016)									X				
[78] Schiel (2018)	X												
[79] Serrou et al. (2014)					X								
[80] Singh et al. (2016)			X										
[81] Subzwari and Nasir (2015)						X							
[82] Thepsatidsilph (2015)						X	X						
[83] Tong et al. (2011)												X	
[84] Trueman et al. (2010)				X									
[85] Tzeng et al. (2008)		X											
[86] Urias (2017)												X	
[87] Vogler et al. (2014)		X	X										
[88] Weraikat et al. (2016 a)		X	X										
[89] Weraikat et al. (2016 b)			X										
[90] Wyld and Jones (2007)						X							
[91] Xie and Breen (2012)		X											
[92] Xie and Breen (2014)								X					
[93] Ziance (2008)							X						

(1) Improving quality control and management inventory in supply chain;
(2) Improving collaboration and coordination in PSC;
(3) Implementing mathematical models for collaboration improvement, costs minimization, uncertainty reduction; (4) Adopting top technologies production and traceability (4.0 manufacturing and RFID); (5) Reducing transportation and storage;
(6) Creating or improving regulatory standards for returns monitoring;

(7) Improving action against counterfeiting; (8) Extending medicines shelf life;
(9) Educating health professionals and consumers for prevention of incorrect EOU/EOL-M discharge; (10) Improving procurement processes; (11) Improving quality of prescriptions and communication between physicians and patients;
(12) Improving RL systems; (13) Creating protocols for correct medicines discharges.
All blanket spaces for a source means “information not available on this subject”.

Appendix J - Barriers of the forward PSC chain that impact EOU-M CE

Identified constraints of the forward PSC processes that impact PSC reverse flows (see caption below) **Sources**	1	2	3	4	5	6	7	8	9	10	11	12
[94] Alhamad et al. (2018)	X											
[95] AlSamanhodi et al. (2017)		X							X			
[96] Andrews et al. (2010)							X					
[97] Bange and Morgan (2018)		X			X	X						
[98] Bekker et al. (2017)									X	X		
[99] Connelly (2018)			X									
[100] Daniszewsi et al. (2002)										X		
[101] De Filippis et al. (2012)				X								
[102] Gyanendra et al. (2011)			X									
[103] Hampson and Ottey (2015)									X		X	X
[104] Jesson et al. (2005)									X			
[105] Jimenez-Gonzalez et al. (2011)						X	X					
[106] Kane et al. (2018)				X				X				
[107] King et al. (2018)										X	X	X
[108] Koenig et al. (2018)					X							
[109] Latif et al. (2013)									X		X	X
[110] Lorenzini et al. (2017)	X	X		X								
[111]McRae et al. (2016)												X
[112] Mwencha et al. (2017)			X									
[113] O'Leary et al. (2006)			X									
[114] Petty et al. (2014)										X	X	X
[115] Rees (2011)	X		X		X		X					
[116] Shah et al. (2014)									X			X
[117] Søndergaard et al. (2006)		X	X									
[118] Taitel et al. (2012)										X	X	
[119] Taylor (2010)								X		X	X	X

[120] Taylor (2014)								X		X	X	X
[121] Toh and Chew (2016)			X					X				
[122] Twigg et al. (2015)										X		X
[123] West et al. (2014)						X						
[124] West et al. (2015)									X			
[125] White et al. (2010)									X	X		
[126] Ze-hua et al. (2011)						X						
[127] Zhang (2017)					X							

(1) Quality assurance of the product; (2) Constraints of forecasting/variability of product; (3) High prices of medicines; (4) Technological barriers;
(5) Need of high amount of R&D investments;
(6)Environmental impacts of production/use of products;
(7) Need for green chemistry initiatives;
(8) Safety concerns/risks for patients; (9) Patients behaviours (over-collection, self-management); (10) Therapy/treatment change; changes in medical conditions; (11) Prescription duration versus change in patients conditions; (12) Lack/failures in monitoring of prescription by pharmacist or other healthcare professional.

Appendix K - Where EOU-M CE takes place in PSC

Stage of the PSC in which the CE is identified (see caption below) **Sources**	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]
[94] Alhamad et al. (2018)				X				
[95] AlSamanhodi et al. (2017)							X	
[96] Andrews et al. (2010)							X	
[97] Bange and Morgan (2018)							X	
[98] Bekker et al.(2017)			X	X	X			
[99] Connelly (2018)				X				
[100] Daniszewsi et al. (2002)			X					
[101] De Filipis et al. (2012)							X	
[102] Gyanendra et al. (2011)			X					
[103] Hampson and Ottey (2015)					X			
[104] Jesson et al. (2005)			X					
[105] Jimenez-Gonzalez et al. (2011)	X							
[106] Kane et al. (2018)							X	
[107] King et al. (2018)					X			
[108] Koenig et al. (2018)	X							
[109] Latif et al. (2013)			X					
[110] Lorenzini et al. (2017)		X						
[111] McRae et al. (2016)						X		
[112] Mwencha et al. (2017)				X				
[113] O'Leary et al. (2006)						X		
[114] Petty et al. (2014)					X			
[115] Rees (2011)								X
[116] Shah et al. (2014)					X			
[117] Søndergaard (2006)						X		
[118] Taitel et al. (2012)			X					

[119] Taylor (2010)					X			
[120] Taylor (2014)					X			
[121] Toh and Chew (2016)						X		
[122] Twigg et al. (2015)							X	
[123] West et al. (2014)			X		X			
[124] West et al. (2015)			X		X			
[125] White et al. (2010)			X		X			
[126] Ze-hua et al. (2011)								X
[127] Zhang (2017)	X							

[1]Upstreaming the chain, in medicines production;
[2]Between pharmaceutical industry and package supplier;
[3] Between patients and pharmacists;
[4] Between pharmacists, patients and needy people;
[5] Between patients, physicians or other health professionals (nurses);
[6] Between several sources of EOU-M donations and a health clinic;
[7] During or after the patients' consumption;
[8] All over the supply chain.

Appendix L - Recommendations for EOU-M CE improving in PSC

What the reviewed studies recommend for improving PSC CE? (see caption below) **Sources**	1	2	3	4	5	6	7	8
[94] Alhamad et al. (2018)		X						
[95] AlSamanhodi et al. (2017)				X				
[96] Andrews et al. (2010)	X							
[97] Bange and Morgan (2018)							X	
[98] Bekker et al. (2017)								
[99] Connelly (2018)						X		
[100] Daniszewsi et al. (2002)				X				
[101] De Filippis et al. (2012)	X							
[102] Gyanendra et al. (2011)			X		X			
[103] Hampson and Ottey (2015)				X				
[104] Jesson et al. (2005)				X				
[105] Jimenez-Gonzalez et al. (2011)	X							
[106] Kane et al. (2018)	X							
[107] King et al. (2018)				X				
[108] Koenig et al. (2018)	X							
[109] Latif et al. (2013)					X			
[110] Lorenzini et al. (2017)								X
[111] McRae et al. (2016)		X	X					X
[112] Mwencha et al. (2017)		X						
[113] O'Leary et al. (2006)								
[114] Petty et al. (2014)				X				

[115] Rees (2011)	X	X	X					
[116] Shah et al. (2014)				X	X			
[117] Søndergaard (2006)								
[118] Taitel et al. (2012)				X				
[119] Taylor (2010)				X				
[120] Taylor (2014)					X			
[121] Toh and Chew (2016)						X		
[122] Twigg et al. (2015)				X				
[123] West et al. (2014)		X						
[124] West et al. (2015)		X				X		
[125] White et al. (2010)		X		X				
[126] Ze-hua et al. (2011)	X							
[127] Zhang (2017)	X							

(1) Improving investments and capacity building in cleaner production, green chemistry and related technologies;
(2) Improving capacity building of health professionals;
(3) Improving communication between patient and health professionals; (4)Improving management and monitoring of prescription by pharmacists or other health professionals (quantities, duration etc); (5) Creating campaigns for patients' education in EOU-M handling;
(6) Creating protocols for EOU-M management;
(7) Customizing medicines to patients;
(8) Improving packaging.