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# Alternative societal solutions to pharmaceuticals in the aquatic environment

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ABSTRACT

Environmental contamination with pharmaceuticals is widespread, inducing risks to both human health and the environment. This paper explores potential societal solutions to human and veterinary pharmaceuticals in the aquatic environment. To this end, we adopt transition research's multi-level perspective framework, which allows us to understand the dynamics underlying pharmaceutical emissions and to recognize social and technical factors triggering change. Our qualitative analysis is based on data collected through literature research and interviews with actors from pharmaceutical industry, the health and agricultural sector. The research aims at identifying potential future solutions including requirements for as well as barriers to pathways leading to these solutions and describing the role of key actors involved. The three alternative societal solutions identified are: 1) accepting pharmaceuticals in the environment - substantial changes to the system are not required; 2) reconfiguring the current system by implementing various innovations that reduce pharmaceutical emissions; 3) fundamentally changing the current system to (largely) avoid pharmaceutical emissions. The paper further elicits societal, financial, organizational, regulatory and technological requirements that can facilitate implementation of these solutions. This work is novel as it constitutes a systemic view on all stages of the pharmaceutical lifecycle, comprehensively synthesizing options and measures along the entire lifecycle into societal solutions that are framed as transition pathways. Deriving societal solutions from key actor's perspectives is innovative and provides insights to reflect on choices societies are going to have to make regarding pharmaceuticals in the environment.



## 1. Introduction

Around the globe, pharmaceuticals along with their metabolites and transformation products are frequently found in the aquatic environment (Aus der Beek et al., 2015). Besides ecotoxicological effects on different plant, fish and bird species emerging from pharmaceutical exposure (Aus der Beek et al., 2015), pharmaceutical residues are found in drinking water (Leung et al., 2013) and food products (Boxall et al., 2006). Furthermore, antimicrobial resistance associated with the presence of antibiotics in the environment is a global threat (Singh et al., 2019). Since both, human and veterinary pharmaceutical use continue to increase globally (due to population growth, rising per capita consumption and growing livestock) the issues are likely to exacerbate (Klein et al., 2018; Van Boeckel et al., 2015).

Pharmaceuticals are potentially emitted into aquatic environments along each step of their lifecycle - from manufacturing via application to disposal. At manufacturing sites, pharmaceutical discharges can be emitted directly to water bodies (Larsson, 2014). After consumption, fractions of administered pharmaceuticals are excreted (Winker et al., 2008). Pharmaceuticals excreted by humans are typically discharged into sewers first, before entering

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receiving waters as point sources (Hughes et al., 2013). Fractions excreted by animals reside in manure that can be spread on agricultural land as fertilizer (Kümmerer, 2008a). From there they can enter the aquatic environment through runoff or leaching (Sarmah et al., 2006). Finally in the disposal stage, inaccurate discarding practices can lead to pharmaceutical pollution of freshwaters (Vollmer, 2010).

Aus der Beek et al. (2015) compile data from numerous studies that proof pharmaceutical presence in different aquatic media. Depending on the compound, geographical location and emission source, hotspots for pharmaceutical concentrations have been identified at e.g. manufacturing sites (Larsson, 2014), wastewater discharges from households or hospitals (Aus der Beek et al., 2015) and areas with intensive livestock industry (Menz et al., 2015).

Pharmaceutical's individual physicochemical, pharmacological and biological properties – and therefore their environmental behaviours – vary widely (Kümmerer, 2008a). With several thousand pharmaceutical substances authorized to the European market (European Medicines Agency, 2020; Kümmerer, 2008a), environmental impact of the manifold substances is extremely diverse.

Previous research focussed on environmental, chemical and technological aspects of pharmaceuticals in the environment (PIE), rather than societal ones (Daughton, 2016). Frequently discussed solutions to PIE focus on removing pharmaceuticals from wastewater through improved treatment technologies. These have proven to effectively remove a variety of pharmaceuticals, where often the degree of removal depends on the intensity or reaction time of the method (e.g. for ozonation or activated carbon) (Mansour et al., 2018; Paucar et al., 2019; Szabová et al., 2020). Nevertheless, this focus is criticized in the scientific discourse, as until now no individual end-of-pipe technology has proven to sufficiently eliminate all substances (Kümmerer, 2008b; Voigt et al., 2020), there is no adequate knowledge about (long term) ecotoxicological risks for remaining effluent concentrations even if removal rates are high (Angeles et al., 2020), and doubts are raised over it's added costs, feasibility and reasonability (Eggen et al., 2014; Kosek et al., 2020; Voigt et al., 2020). Moreover it is unclear if current technologies can remove prospectively developed substances or compounds that are created during treatment processes (Kosek et al., 2020; Kümmerer, 2008b). Besides, technological end-of-pipe solutions do not address the issue of PIE over the entire lifecycle and neglect approaches that relate to societal aspects of how pharmaceuticals are prescribed, used, and disposed.

We argue that including the societal dimension into the discussion is essential, as the way society utilizes pharmaceuticals drives environmental emissions along the entire pharmaceutical lifecycle. Society must find a way to deal with trade-offs between improving human and animal health through pharmaceutical use and environmental sustainability.

To date, comprehensive studies that include societal embedding of proposed solutions are lacking. In particular, there is a clear knowledge gap in addressing appropriate institutional settings, economic, cultural and behavioural incentives and actors' collaborations towards successful strategies.

In this paper we explore alternative societal solutions to deal with PIE by using the multi-level perspective (MLP), a framework that conceptualizes patterns for system change at different analytical levels (Geels, 2011). A societal function (in this case pharmaceutical supply and use) is performed by a socio-technical system, an established configuration. Changes of the existing system occur due to developments and interplay at the different levels. We perform actor interviews and enrich as well as cross-check these with comprehensive literature to delineate different future solutions, following MLP theory. The core of the paper is to inspect actors' perceptions of the situation regarding PIE and identify their understanding and visions on solutions, their ideas regarding actor roles, and their opinion on requirements to implement solutions. Further, we explore what barriers actors foresee for each solution. Interviews were conducted in Germany and the Netherlands. While the research's scope is on the aquatic environment, the topic was framed towards interviewees as PIE in general.

## 2. Theoretical framework, methods and data

### 2.1. Multi level perspective framework

This study uses the MLP to describe and analyse alternative societal solutions to PIE. The framework originates from transition research, which investigates system changes over time. MLP considers the setting in which transitions occur as a socio-technical system (Geels and Kemp, 2012), which is framed as the pharmaceutical lifecycle from development to environmental emission in this study.

Embedded in the socio-technical system, the MLP differentiates between three analytical levels landscape, regime and niche (Geels, 2011). A conceptual overview of the MLP, including the contextualization of the pharmaceutical lifecycle, is illustrated in Fig. 1.

The regime level is assigned to the space where actors interact, maintaining the setting of the socio-technical system according to anchored rules that determine the functioning of the system. It represents a complex arrangement of social groups and actors related to the system's societal function (Holtz et al., 2008). In this research we specifically focus on actor groups related to the societal function of pharmaceutical supply. Niches refer to emerging innovations that might prevail (Geels and Kemp, 2012). In the context of pharmaceutical lifecycle, both technical and non-technical innovations reducing PIE are considered. The landscape is the exogenous context within the socio-technical system including the natural environment, material components like infrastructure and societal components such as legal structures, cultural believes and political trends (Geels, 2002). With the core of this research being on alternative societal solutions to PIE, we focus on the societal components of the landscape level by describing and interpreting policy developments in the EU along with Germany and the Netherlands as cases where regime actors were interviewed. In addition, we outline landscape changes mentioned by the interviewed regime actors.

Geels (2011) and Geels and Schot (2007) describe transitions as shifts from one regime to another whereby the landscape and niche levels are derived concepts in relation to the regime. Landscape dynamics creating pressure on the regime and occurring innovations at niche level can create momentum for a transition (Geels and Schot, 2007). This research uses the MLP to structure what alignments of changes at the different levels can lead to distinct futures regarding PIE. A detailed description of these pathways is presented in the SI.

### 2.2. Data collection

Data from regime actors was collected through 15 semi-structured interviews. Even though this research investigates the system of the pharmaceutical lifecycle as a whole, interviewees were specifically selected from pharmaceutical industry, the healthcare and agricultural sector as these are considered to play a pivotal role in the pharmaceutical supply as well as in a potential transition process. The participants were selected after the principles focus group and snow-ball sampling as outlined by Reed et al. (2009); this is described in the SI. The interview was clustered into six sections: (i) participant background; (ii) today's situation and problem description regarding PIE; (iii) future and potential

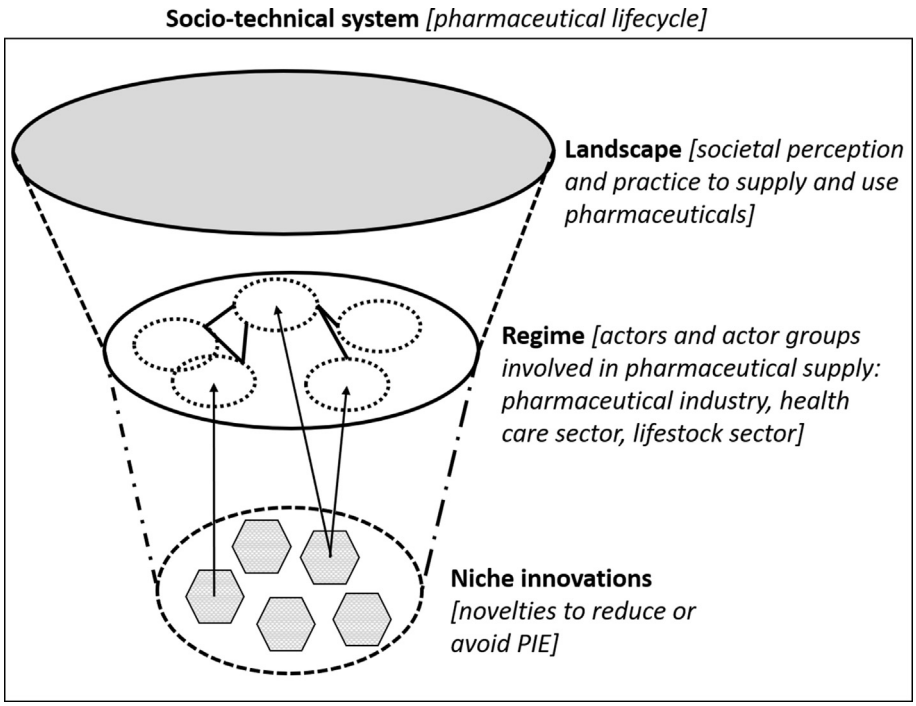


**Fig. 1.** Conceptual overview of the Multi-Level Perspective illustrating the three analytical levels landscape, regime and niches of the socio-technical system in context of the pharmaceutical lifecycle, adapted from Geels (2002).

solutions regarding PIE; (iv) requirements on landscape and niche level for potential solutions; (v) responsibilities for potential solutions; (vi) critical reflection on solutions. The interview manuscript can be found in the SI.

Pertinent literature was studied to gain insight on developments at niche, regime and landscape level, complementing and cross-checking interview data. This resulted in an inventory of existing niche innovations, an outline of current regime dynamics and a description of ongoing societal landscape changes.

### 2.3. Interview analysis

All interviews were transcribed non-verbatim and coded for qualitative analysis with assistance of atlas.ti software. Codes were created upon the different sections outlined under 2.2. We extracted code reports to thematically analyse today's situation as well as alternative societal solutions to PIE. To delineate these, the theory of transition pathways by Geels and Schot (2007) was followed (see SI). Each interview contributed to sketch alternative future regimes, whereby each future regime is based on input from multiple interviewees and from literature. As the study is qualitative, we do not weigh alternative solutions, but rather elicit actors' perspectives on different options and pathways.

## 3. Results

### 3.1. The current socio-technical system of the pharmaceutical lifecycle

#### 3.1.1. Landscape changes affecting pharmaceuticals in the environment

First legal steps concerning PIE were introduced by the EU in 1995 when requesting environmentally relevant information for market authorization of new pharmaceutical products. Nonetheless, only in 2005 information requirements were specified, avoiding the previously insufficient environmental risk assessments (ERA) (Wennmalm and Gunnarsson, 2010). In case of expected high environmental impacts, legislation differentiates between human and veterinarian pharmaceuticals. Authorization of the former is not affected by high environmental risk as EU guideline 2001/83/EG states this cannot impact the risk-benefit consideration (Koschorreck and Hickmann, 2008; Parliament and Comission, 2001). Still, measures to minimize environmental risks should be taken, if possible. A high environmental risk from veterinary pharmaceuticals can obstruct market release in two cases: environmental risks cannot be minimized and a comparable compound is available (Koschorreck and Hickmann, 2008). These landscape developments show that human health is prioritized over environmental health. However, animal health is not generally prioritized over environmental health.

The first grounds for European water legislation emerged in the 1970s with e.g. water quality standards for drinking water abstraction. An important transformation took place decades later by implementing the Directive 2000/60/EC, commonly known as Water Framework Directive (WFD). Implemented in 2000, the WFD represents a fundamental guideline for European water management, specifically considering pollution prevention (European Commission, 2016b). However, pharmaceutical pollution is not explicitly mentioned. To complement EU water management, a watch-list for emerging water pollutants was implemented under the WFD in 2015, intended to provide targeted, high-quality information on substances of concern (European Commission, 2016a). The list is iteratively evaluated, whereby substances are added and removed. The watch-list comprised the first link of pharmaceutical pollution to EU water legislation. Barbosa et al. (2016) conclude that despite legislative developments under the WFD, legal discharge limits for pharmaceuticals are lacking.-Whereas the WFD targets freshwaters' quality status independent of the emission sources, water pollution through pharmaceutical production is additionally addressed in Directive (2010)/75/EU

known as industrial emissions directive. It demands the inclusion of environmental limit values when giving industrial permits (European Commission, 2019b). Given the non-existence of EU limit concentrations for pharmaceuticals, these must be established by the permitting authority in coherence with experts' best available technique reference document. Environmental inspections are implemented as a control mechanism (European Commission, 2019b). Additionally, in 2013 the EU enforced that all imported pharmaceutical ingredients have to be produced with respect to good manufacturing practices by EU standards (European Commission, 2012).

Addressing PIE for the first time from a lifecycle perspective in policy, the European Commission published a strategic approach to PIE in 2019. The approach provides different areas of action along the pharmaceutical lifecycle, to be followed by the EU and it's member states (European Commission, 2019a). Nevertheless, the approach neither presents discharge limits nor quantifiable targets for proposed actions. On national level, the Dutch government developed a chain approach to address PIE from a lifecycle perspective, releasing an implementation program in 2018. The program outlines different actions to reduce human pharmaceutical emissions. Veterinary pharmaceutical emissions are not (yet) part of the approach (Government of the Netherlands, 2019). In Germany, no governmental policy exclusively tackles PIE. However, governmental bodies initiated a stakeholder dialog that developed a strategy to implement measures reducing trace pollutants in waters (BMU and UBA, 2019). Policy developments along with other landscape changes mentioned by regime actors are displayed in Table 1.

### 3.1.2. Regime dynamics affecting pharmaceuticals in the environment

**Pharmaceutical development and manufacturing:** The required ERA for market authorization (section 3.1.1) forces regime actors to consider environmental aspects in pharmaceutical development. Nevertheless, interviewees described potential neglection of the total environmental loads through the product-based approach and the lack of follow-up after authorization as shortfalls of the existing ERA. The pharmaceutical developing sector was mentioned to give priority to human over environmental wellbeing. Likewise, in ERA legislation environmental risks cannot lead to exemption from authorisation. Regime actors explained that drivers for pharmaceutical development are the discovery of substances resulting in first-ever treatment of diseases, and of products preferable over existing pharmaceuticals, e.g. fewer side effects. Economic interest significantly drives the development of new pharmaceuticals, as mentioned for antibiotics by various interviewees. Little research is conducted to develop new antibiotics, which would likely be classified as reserve medication in case of patients' resistance towards common antibiotics. This classification potentially results in prescription restrictions, limiting profit margins irrespective of development costs. The latest AMR industry alliance report describes a challenging overall economic environment for researching companies and proposes financial incentives from governments as a solution (AMR Industry Alliance, 2020).

Environmentally beneficial dynamics of the pharmaceutical developing sector cover vaccine developments or the recent focus on biopharmaceuticals. Alongside, Taylor (2016) describes synergies between drug design criteria and positive environmental significance, e.g. full oral adsorption leading to less excreted fractions. Further, regime actors agreed that the sector respects the environmental relevance of pharmaceuticals, also because the topic was recognized as highly media-effective and therefore politically relevant.

The relevance of image was as well mentioned for the manufacturing industry. One interviewee described that scoring well in environmental rankings is positively received by shareholders. Further, participants portrayed the industry's increasing awareness of their responsibility after several reports were doubting responsible manufacturing. However, pharmaceutical manufacturing happens along global production chains, complicating implementation and control of ubiquitous sustainability criteria. On global level, industrial discharge limits are rare (Larsson, 2014). Regulations exist within the EU (section 3.1), but most pharmaceutical manufacturing takes place outside Europe (Larsson, 2014). Interviewees from the health and agricultural sector were strongly concerned about pollution from manufacturing, especially outside the EU. Nevertheless, technological developments for industrial wastewater treatment exist along with self-regulation by the industry (AMR Industry Alliance, 2020; Larsson, 2014).

**Human health sector:** The sector's core priority is curing humans, commonly using allopathic medicine. According to regime actors, medicine use is promoted by pharmaceutical industry, governments, doctors' and pharmacists' organization, denoting non-transparent dynamics. One interviewee explained that critical considerations exist on the functioning of certain pharmaceuticals (where effects are statistically significant, but not clinically relevant), but is generally not shared by doctors. Another identified mechanism supporting medicine use is the patients' amenity to prefer medical prescriptions over behavioural change to improve well-being. This is similar to humans endorsing environmental cautiousness, but not acting accordingly themselves - a value-action gap well-known in environmental research (see e.g. Kollmuss and Agyeman (2002)). Moreover, medical staff is not intrinsically aware of PIE, misperceptions towards wastewater treatments' effectiveness exist and dealing with PIE is perceived to surpass their responsibility. Nevertheless, regime actors also observed emission limiting dynamics within the health sector. They described increasing media-reporting about PIE, raising awareness among staff and patients. Specifically for the Netherlands, a trend towards less surgeries and de-prescribe medicines was observed.

Pharmaceutical leftovers potentially leading to environmental emissions exist in healthcare institutions and private households (Daughton and Ruhoy, 2011). Interviewees mentioned prescription routines leading to leftovers and criticised the absence of unified, safe disposal systems.

**Agricultural sector:** Pharmaceutical use in livestock is practiced to avoid and treat diseases in animals used for animal production.

**Table 1**
Landscape changes determined through regime actor interviews.

| Landscape element | Influential changes |
|---|---|
| Policy | Regulative developments regarding PIE |
| Demographics | Aging population in Europe increases medicine use |
| Migration | Increasing medicine use due to re-introduction of previously controlled diseases |
| Societal trend | Societal pressure to decrease animal numbers (specifically mentioned for the Netherlands) |
| Societal trend | Society demands animal production under high animal welfare standards, increasing use of certain pharmaceuticals |

Besides therapeutic use, there is use for prophylaxis, growth promotion and increased production efficiency (Bloom, 2004). In the EU, growth promotion with pharmaceuticals was prohibited in 2006 (European Commission, 2005). Where economic competitiveness is a main driver for the agricultural sector (Sarmah et al., 2006), a more efficient production leads to more financial profit and stability. Limiting disease spread and having healthy animals is a key to this strategy (Sarmah et al., 2006). Regime actors described different dynamics analogous to efficiency, driving environmental emissions of pharmaceuticals. One of these is the economic trade-off between treating diseases once they occur and prevention through vaccines or management practices. Another is the economic decision to preventively treat the entire herd to avoid disease spreading once an individual is infected. Sarmah et al. (2006) closely link big animal numbers on farms to medicine use controlling disease spread. However, interviewees indicated that conditions and treatment practices differ among animal types and farming systems, causing differences among farms. Yet, there is no information available on pharmaceutical use intensity differentiated between farming systems, farm sizes or animal types, impeding comparisons. One participant explained that antibiotic use on organic farms is highly restrictive, as it is also regulated by the EU (Ivemeyer et al., 2012), but organic farm animals spend more time outside, making them more vulnerable to certain health issues. Another trend described is increasing farm productivity as farm size and degree of specialization grows. Interviewees observed the phenomenon that regional hotspots of large, highly specialized farms cause high animal densities and pollution potential where the animal products are exported from that region. Regime actors were also critical on the fact that veterinarians prescribe and sell pharmaceuticals providing them a financial prescription incentive.

Discussions of veterinary pharmaceuticals in the environment strongly focus on antibiotics. Several regulations, e.g. reporting of medicine application, is only required for antibiotics, possibly causing overlooking the relevance of other substance groups.

#### 3.1.3. Niche innovations

Niches where innovations reducing PIE occur developed along the entire pharmaceutical lifecycle. Fig. 2 illustrates existing niche innovations with overall descriptions per innovation identified. For some niche innovations multiple approaches have been discovered (e.g. different pharmaceutical removal technologies are summarized as “advanced wastewater treatment”). An overview of niche innovations, including alternative approaches is presented in the SI.

### 3.2. Potential societal solutions

Three alternative societal solutions were identified: 1) Accepting pharmaceuticals in the environment as a reproduction process without regime shift; 2) Implementing niche innovations in different sectors as a reconfiguration pathway where a new regime emerges from the existing regime, hereby regime actors remain; 3) A system change as a de-alignment of the current regime, potentially with re-alignment of an entirely new regime. Fig. 3 gives an overview of the three identified solutions, embedding case-specific items into the concepts of different transition pathways.

**Accepting pharmaceuticals in the (aquatic) environment:** From an environmental risk perspective, pharmaceutical substances bear identical risk as any other chemical. From an environmental management viewpoint however, health benefits distinguish pharmaceuticals from other chemicals (Taylor, 2016). Regime actors reflect this opinion by describing that pharmaceutical emissions are inevitably in guaranteeing human and animal wellbeing. We therefore identified the first future solution as “accepting pharmaceuticals in the environment”, a reproduction of the current regime. Especially regime actors of the pharmaceutical industry and the human pharmaceutical sector pointed out that society would always prioritise pharmaceutical use over their environmental relevance. Consequently, they believe that the societal perception of pharmaceutical’s importance (section 3.2) will not change, preserving existing regime dynamics. Other interviewees were convinced that options to reduce pharmaceutical use exist, but are not entirely avoidable due to serious diseases such as cancer. Hereby, they suggested to follow a no-regret strategy, where avoidable emissions are reduced without trade-offs. Requirements mentioned for this approach are evidence on environmental risk and knowledge about emission sources of pharmaceuticals.

**Implementing niche innovations:** Interviewee statements for this solution varied from individual innovations to broad sets of measures for complementary or parallel implementation. An overarching innovation mentioned by most participants is awareness raising, involving education and knowledge transfer. Awareness raising is perceived as relevant to increase public understanding of the topic, but also to equip actor groups with knowledge to implement other innovations. A comprehensive list of awareness-raising elements and their requirements is given in the SI.

The so-called green pharmacy is a frequently discussed approach to PIE, which interviewees considered relevant as well. Firstly, they referred to the design of new substances while considering environmental biodegradability. Where pharmaceuticals are stable within the target body fulfilling their function, they degrade during wastewater treatment or in the environment (Straub, 2016). Kümmerer (2019) describes different methods resulting in more environmentally friendly β-blockers, antibiotics and one cytostatic. Secondly, multiple regime actors suggested the enhanced development of nature-based pharmaceuticals and phytotherapeutics. Literature introduces these concepts as “benign by nature” (Straub, 2016), where synthetically developed pharmaceuticals are substituted by natural compounds not showing environmental toxicity. One example is alkaline phosphatase, a naturally-occurring enzyme preventing inflammations (Seinen and Feil, 2019). Thirdly, participants mentioned new dosage forms where the same effect is achieved with smaller substance amounts. Pharmaceuticals with low bioavailability require high administered doses to reach pharmaceutically active concentrations, leading to large excreted fractions (Straub, 2016). So-called prodrugs are inactive in their original form. After administration, prodrugs metabolize and become pharmacologically active. This leads to reduced doses, increased bioavailability and smaller excreted fractions (Straub, 2016). Lastly, regime actors explained that vaccine development can reduce pharmaceutical use and emissions.

Regarding drug authorization, one interviewee argued for improving the existing ERA. Another participant pleaded to exclusively authorize pharmaceuticals that proof to have more clinically relevant effects than placebos and remove non-complying substances from the market.

Interviewees named a series of requirements to realize development-related innovations:

- societal and sectoral demand
- research unbiased as to the result
- willingness by pharmaceutical industry
- new orientation of pharmaceutical industry
- financial and legislative governmental research support to incentivise
- governmental enforcement
- enforcement by health insurance companies

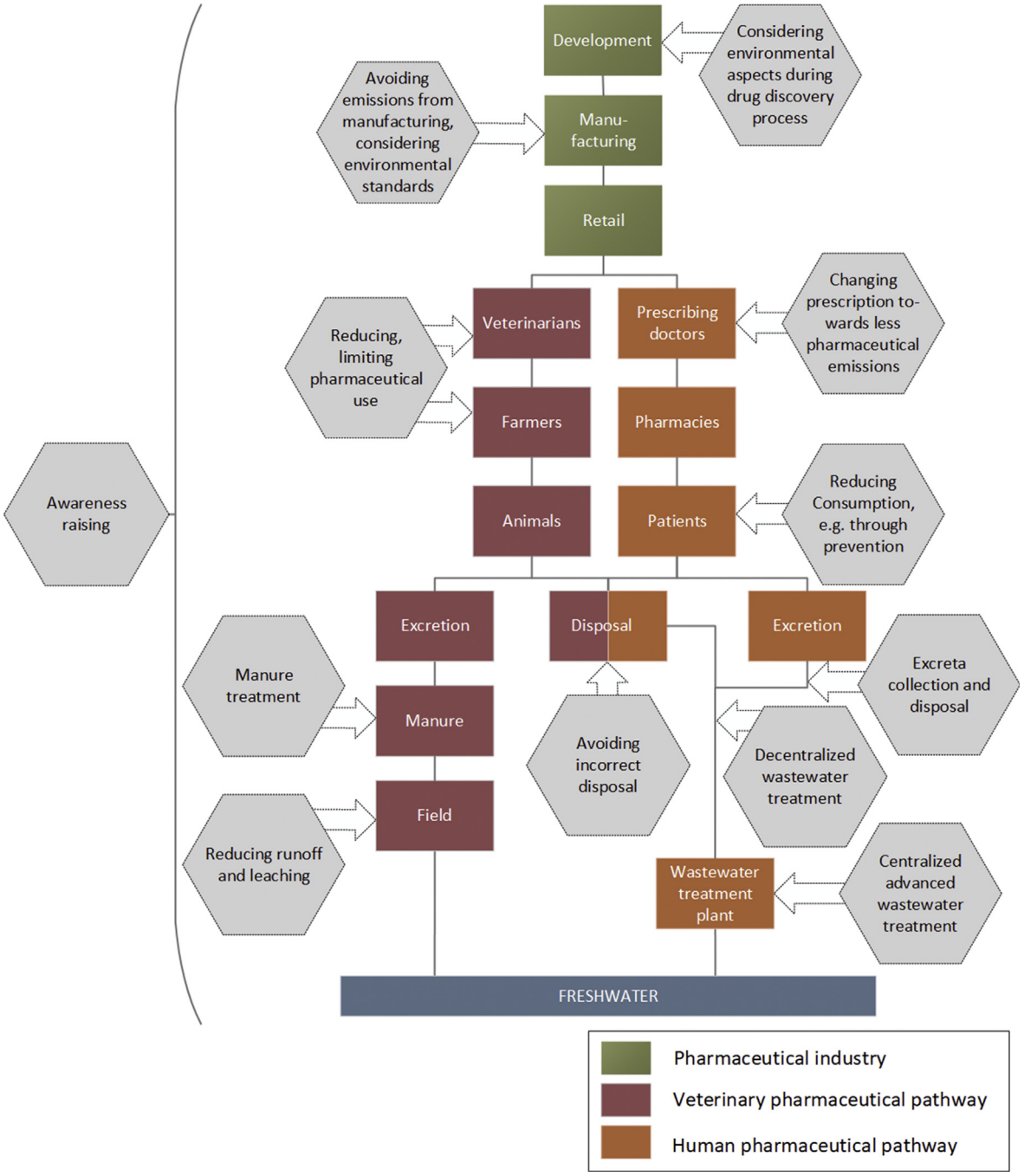


**Fig. 2.** Pharmaceutical lifecycle from the development to disposal, and niche innovations (in hexagons) illustrating where they have an effect.

- taxation to incentive sustainable pharmacy

Coherently with literature (Larsson, 2014), participants considered the reduction of emissions from manufacturing alongside with the implementation of environmental standards as essential for the industry. This requires research-based standards and technologies to safely dispose industrial pharmaceutical wastes or treat wastewaters. To guarantee that manufacturers meet standards, one participant suggested a "carrot and stick approach": Incentivizing and rewarding well-performing manufacturers on the one hand, enforcing and sanctioning poorly-performing companies on the other hand. Additionally, one interviewee suggested to move all pharmaceutical production to Europe, where supposedly environmental requirements are stricter.

Another set of niche innovations targets the supply and use of human pharmaceuticals. Participants agreed that pharmaceutical use, thus emissions, can be reduced through lifestyle interventions such as reducing weight, eating healthy, physical activity. Deffner and Götz (2008) likewise describe health-supporting measures to reduce PIE arguing for prescribing and financially supporting these through the health care system. Requirements for lifestyle interventions found are:

- public education
- motivation among people
- promoting lifestyle interventions instead of pharmaceutical use

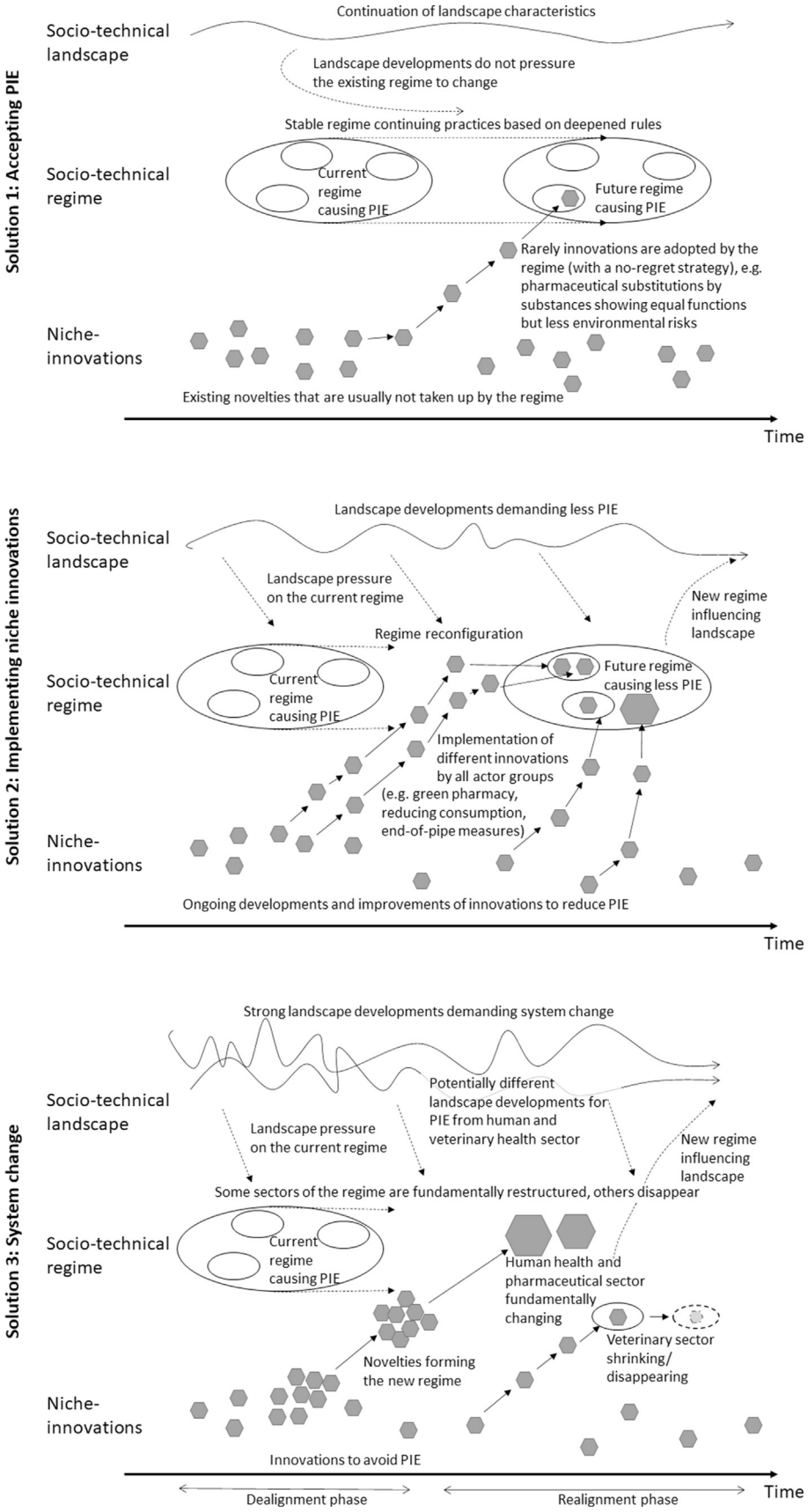


**Fig. 3.** Transition pathways for different societal solutions to pharmaceuticals in the environment (PIE), from top to down: 1) accepting PIE, 2) implementing niche innovations, 3) system change. Adapted from Geels and Schot (2007).

- rewarding system for good performance
- regulatory measures on unhealthy products (taxing, restricting accessibility)

Moreover, regime actors argued for the implementation of niche innovations related to prescription and use of pharmaceuticals: Changing prescription routines, using pharmaceuticals appropriately, alternative treatments. A list describing detailed elements and their requirements is presented in the SI. In Sweden, these niches were adopted by the regime through environmental classification of pharmaceuticals, supporting practitioners to choose alternative pharmaceuticals posing less environmental risk (Ågerstrand et al., 2009).

Estimates on incorrectly disposed leftover pharmaceuticals differ strongly (from 0% in Sweden to 92% in the U.S.) and continuous monitoring about pharmaceutical discarding is lacking (Vollmer, 2010). Numerous participants of this study see incorrect disposal as an ongoing issue. They named smaller package sizes and pharmaceutical recycling as innovations to reduce pharmaceutical leftovers. For remaining leftovers, they stressed the need for safe and ubiquitous disposal systems, advertised through public media and pharmacies.

Moreover, regime actors mentioned that end-of pipe innovations can contribute to this solution, whereby they differentiated between decentral and central pollution control technologies. Decentral innovations covered installations in household toilets, wastewater treatment at healthcare institutions or urine collection systems. Several such ideas are elaborated in literature, e.g. contrast agent collection with urine bags (Niederste-Hollenberg et al., 2018). Interviewees listed following requirements:

- technological developments for household installations
- focus on specific pharmaceuticals for urine collection
- urine collection must be feasible for patients
- case by case decisions about most suitable system
- innovation funding; decision on who covers costs

Centralized installations removing pharmaceuticals at municipal wastewater treatment plants are perceived as useful complements to source-oriented innovations. This approach has been intensively researched – considering numerous technologies including ozonation, activated carbon or membrane filtration (Fröhlich et al., 2019; Homem and Santos, 2011) - and regionally implemented, for instance in Switzerland (Eggen et al., 2014). Furthermore, these technologies can be effective against metabolites as well (Rúa-Gómez et al., 2012). Given high costs for these technologies, regime actors suggested to focus on hotspots where additional treatment is economically and ecologically useful. They see necessity for funding schemes and propose ascertainment of society's willingness to pay.

Disease prevention was described relevant for the livestock sector as well. Besides vaccines, health-supporting management plays a significant role. Participants stressed the importance of well-managed housing, food and hygiene. These measures are likewise discussed in literature (Klatte et al., 2017). However, understanding the effectiveness of adjusted livestock management on environmental pollution requires further investigation and costs may hamper implementation (Evans et al., 2019). Requirements mentioned by interviewees to overcome these aspects include:

- Knowledge by farmers
- Quality system for farmers
- Broad, coherent animal health data collection for better knowledge on health management (e.g. animal health index)
- Novelties improving health management (e.g. housing)
- Investments on farms
- Higher prices for animal products

Other innovations proposed target the application of pharmaceuticals in livestock. We clustered these as illustrated in Table 2.

Manure treatment and improved soil management were named as end-of-pipe innovations. Besides manure incineration (Derksen et al., 2015), different treatment options such as heating, drying, pasteurisation exist (Vidaurre et al., 2016). Despite these options proposed in literature, interviewees named the development of treatment methods along with loosening legal regulation on manure processing as requirements for this innovation. Soil properties influence pharmaceuticals' leaching and runoff potential significantly (Sarmah et al., 2006), which is why optimized soil management practices (soil cover, optimized organic content, high root density) were described as beneficial. Knowledge about these practices was named as a key requirement.

To avoid incorrect disposal of veterinary pharmaceutical leftovers, one participant proposed that veterinarians collect leftovers from farms and safely dispose them.

**System change:** De-alignment of the current system can occur independently for the human and veterinary sector. For the agricultural sector, different directions of system changes were brought up by the interviewees (Fig. 4, including requirements). Rethinking farming systems and reducing animal numbers are transitions, where the current agricultural sector changes fundamentally. Similarly, Lamine (2011) investigates transition pathways towards ecologization of agriculture. The disappearance of livestock and the ban of pharmaceuticals are transitions where most likely entire sectors disappear.

System change concerning human pharmaceutical emissions was also discussed among regime stakeholders. One participant mentioned the ban of pharmaceuticals as a solution in case society values environmental quality over individuals' human health. This is a rationale where environment as a common good is exploited by pharmaceutical use and correlated pollution of individuals. Giubilini (2019) follows a similar idea describing antibiotic resistance as a tragedy of commons where consequences of individual's antibiotic use affect the entire society. Another interviewee proposed a system change towards categorizing the necessity of treatments distinguishing between life-endangering and lifestyle-influencing situations. Consequently, a variety of currently common treatments would disappear in the future.

### 3.3. Responsibilities and barriers to potential solutions

Interview results indicate that a wide range of actors are responsible for proposed solutions. Individual actors or sectors are seen in charge of implementing innovations within their competence. Governmental institutions were given responsibility to enforce regulations and control mechanisms. Society was described as a driver that can demand and induce change This is a typical landscape change potentially triggering a transition. Several participants pointed out that simultaneous actions by different actors are required to reach proposed solutions. A detailed list of actor groups that regime actors see responsible for the implementation of solutions is presented in the SI.

For the solutions 'implementing niche innovations' and 'system change' regime actors described numerous barriers. Some are specific barriers to individual innovations or requirements; others are overarching hurdles that hinder proposed change. In our analysis, we retrieved financial, knowledge, societal, cultural, responsibility, regulatory, organizational and technological barriers to proposed solutions. A comprehensive overview of barriers is given in the SI.

**Table 2**
Niche innovations targeting pharmaceutical use in livestock plus requirements.

| Niche innovation | Detailed elements | Requirement |
|---|---|---|
| Restricting pharmaceutical use | Restricting substances proven to cause human or environmental health issues<br>Precautionary prohibition of substances not proven to have no environmental or human health risk | |
| Reducing pharmaceutical use | Using reduction potential | • Farmers' and veterinarians' willingness to change routines<br>• Not paying veterinarians for selling medicine, but for keeping animals healthy and for their know-how |
| | Extend benchmarks and measures from antibiotics to all pharmaceuticals<br>Breed more robust animals to decrease use | • enforcement |
| Changing application form | | • legal permission where necessary |
| Alternative treatments | Phytotherapy<br>Homeopathic therapy<br>Natural feed supplements reducing pharmaceutical use | • innovations<br>• knowledge and willingness by veterinarians |

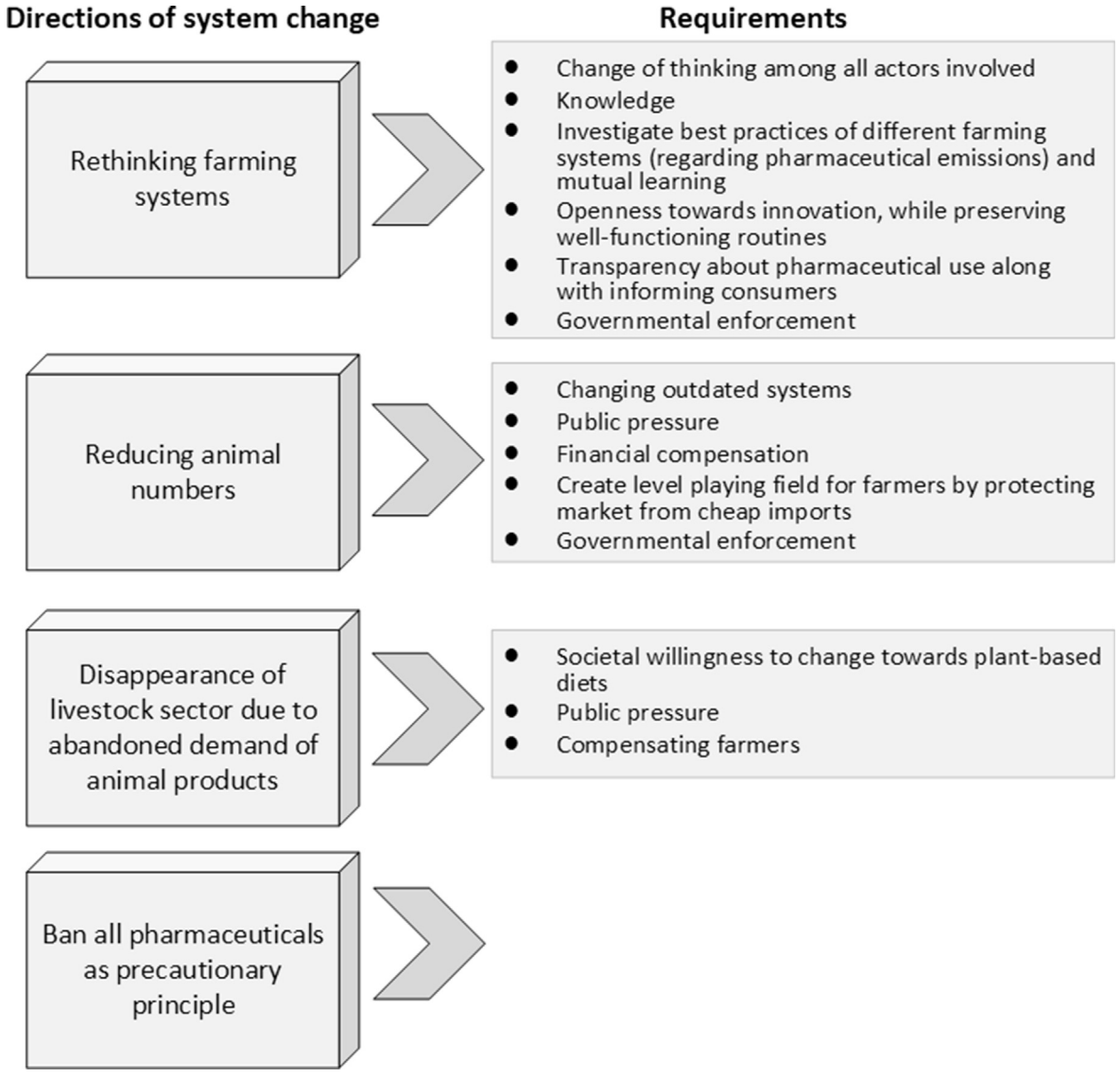


**Fig. 4.** Directions of system changes and their requirements as societal solutions to veterinary pharmaceuticals in the environment, resulting of stakeholder interviews.

## 4. Discussion

### 4.1. Reflection on identified solutions

As checking of results from actor interviews against the existing literature was conducted in the results section, this chapter critically reflects on the pathways of the identified solutions in addition to the results presented.

An established regime of pharmaceutical provision, supply and use is in place. Whilst the human pharmaceutical sector shows lock-ins due to focus on human health over environmental health, the veterinary pharmaceutical sector appears locked in because of rooted (economic) structures. Despite the existence of an established regime, pressuring landscape changes to address PIE alongside with various niche developments were identified. Still, niche innovations are not yet adopted at large scale due to multiple barriers.

Accepting PIE is one identified solution, prospectively not or insignificantly reducing emissions. Expectably, the regime in place is stable, established routines maintain due to lack of societal landscape changes and non-adaptation of innovations. A transition of the socio-technical system is not anticipated. Considering global predictions of rising pharmaceutical use, this solution poses continuous, potentially increasing risk for environmental and human health. This is a contradiction to international agreements such as UN's sustainable development goals (United Nations, 2020) or the strategic approach to pharmaceuticals in the environment by the EU (European Commission, 2019a). Furthermore, it interferes with intergenerational equity. Natural resources are exploited by the current society at the cost of future generations.

Implementing innovations as a solution to PIE covers numerous individual aspects which need simultaneous development to capture the diverse substances and emission pathways. Given their extensive spectrum, emissions are probably reduced, but not avoided as literature indicates the lack of widespread impact of measures (e.g. Straub (2016)). While regime dynamics transform for this solution, the regime of pharmaceutical life cycle and associated actor groups prevail. To achieve this reconfiguration of the existing regime, several barriers, typical lock-in mechanisms (Geels, 2011), have to be overcome (see SI).

A system change can lead to the avoidance of PIE. We identified several types of system change for the human and veterinary pharmaceutical sectors. While some will change or abandon certain regime groups, likely to result in a reduction of PIE, others are more fundamental, resulting in disappearance of entire sectors and emission avoidance. Both constitute a transition where the societal importance of human pharmaceutical use and the consumption of animal products change fundamentally.

Following transition pathway theory, we identified three independent solutions. However, elements of different solutions may be combined, e.g. accepting PIE for specific cases, developing green pharmaceuticals for human treatment and abandoning the livestock sector.

Setting the three solutions in context of ongoing landscape changes, regime dynamics and niche developments (as outlined in sections 3.1.1 to 3.1.3), trends clearly push towards implementing niche innovations. Landscape changes on policy level aim at accelerating innovation adoption, plus niche innovations are increasingly researched. Regime actors indicated their willingness to adopt various niche innovations, if feasible in terms of availabilities, costs, regulations and other requirements (see 3.3). Furthermore, several innovations reducing PIE have been implemented already, according to the regime actors.

Several elements investigated in this research, were discussed and evaluated in previous studies. However, none of these studies consider different options society has as we do in this research. It is novel to analyse the current system with ongoing changes and explore potential future solutions from there.

### 4.2. Limitations of the study

Conducting this study in a European context generated results potentially not universally applicable. Pharmaceutical use patterns vary widely, leading to globally diverging situations (Klein et al., 2018). Additionally, socio-technical systems differ among regions (Coenen et al., 2012). Distinct niche, regime and landscape levels – e.g. different legal frameworks (Maron et al., 2013), wastewater systems (Malik et al., 2015), socio-cultural values of livestock production (Thornton, 2010) - restrict global implementation of proposed solutions. Consequently, requirements for solutions might differ as well. Yet, the research describes a set of solutions providing universal directions even if not all aspects are directly transferable to all world regions.

The research considers the pharmaceutical lifecycle for human and livestock use, excluding pharmaceutical emissions from e.g. aquaculture or orcharding industry (Gaw et al., 2014; McKenna, 2019). Moreover, interviews were limited to regime actors from sectors related to pharmaceutical supply. By defining this scope, we neglect other actor groups being part of the regime in a broader sense, such as patients or water authorities. We recommend that future research enlarges this pool of actor groups. Further, a bias might exist through participant selection and interviewee viewpoints. Participants were mostly contacted through sector-representing organizations. Even though we stressed special interest by interviewees is not required, (unintentional) selection of actors interested in PIE might have occurred. Consequently, this research bases on interviewees' perceptions, which are valid, but not exclusive. More or other dynamics than those captured through the interviews, might exist.

Regime actors described solutions from their viewpoint of today's situation. Some considered future predictions such as demographics. The future is uncertain, however, if conditions, thus landscape, change fundamentally, so may perspectives on solutions. Thornton (2010) described an emerging global pandemic as such incident.

This qualitative study presents alternatives without quantitatively assessing their consequences in terms of economic, societal or environmental effects, which should become subject of further research.

## 5. Conclusion

Different societal solutions to deal with PIE were identified by investigating the pharmaceutical lifecycle through actor interviews and literature, using the MLP framework and it's theory on transition pathways: 1) accepting pharmaceuticals in the environment, 2) implementing niche innovations, 3) system change. They illustrate a wide spectrum of futures in terms of pharmaceutical emissions, regime dynamics and societal changes. Accepting PIE does not require changing the current regime, but pharmaceutical pollution will at best remain, but likely worsen, considering global trends. However, we found it is more likely that a range of innovations is going to be implemented as innovation development occurs in various niches, current regime actors describe dynamics towards implementation of niche developments and societal landscape dynamics such as policy changes push towards this direction. Nevertheless, it is not fully clear (yet) how this will affect PIE. On the other hand, a transition to a new regime, with highly restricted human pharmaceutical use and decimated livestock sector, is expected to result in a substantial effect on PIE. The major

system and sectoral changes needed however, will require societal pressure, governmental enforcement and financial incentives.

This study illustrates how, in the Dutch-German context, society unequivocally prioritises human wellbeing over environmental risks. A fundamental system change for human pharmaceuticals is therefore not to be expected until this deeply rooted perception changes. For the veterinary sector this hierarchy is less pronounced, as landscape developments show. If these developments result in the societal decision to reduce or renounce livestock production as well as the consumption of animal products, this is (in time) expected to reduce animal related PIE.

Exploring alternative societal solutions to PIE while considering the entire pharmaceutical lifecycle and emphasizing the societal dimension is novel in the largely technology dominated discourse on PIE. Requirements for and barriers to changes thus provide a valuable contribution to society at large and decision makers in particular when dealing with PIE.

## CRediT authorship contribution statement

**Lara Wöhler:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft. **Arjen Y. Hoekstra:** Conceptualization, Methodology, Supervision, Funding acquisition. **Rick J. Hogeboom:** Writing - review & editing. **Marcela Brugnach:** Conceptualization, Methodology. **Maarten S. Krol:** Writing - review & editing, Methodology.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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