

## DEVELOPING A CHALLENGES LANDSCAPE RELATING TO DRUG SAFETY, PROVISION, AND DISTRIBUTION IN RESOURCE-LIMITED SETTINGS FOR THE CASE OF HIV/AIDS

B. Huysamen<sup>1\*</sup>, I.H. de Kock<sup>1</sup> & L. Bam<sup>1</sup>

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#### Contact details

\* Corresponding author  
18200648@sun.ac.za

#### Author affiliations

1 Health Systems Engineering and Innovation Hub, Department of Industrial Engineering, Faculty of Engineering, Stellenbosch University, South Africa

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### ABSTRACT

Since 2010, pharmaceutical organisations have begun to provide drug patents in sub-Saharan Africa through the UN Medicine Patent Pool. This initiative allows any pharmaceutical manufacturer to access these patents and manufacture the drugs, thereby aiming to decrease the associated lead times and costs. The participation of numerous manufacturers, some of whom may not have well-established quality control systems in the market, intensifies the need for effective drug quality monitoring. Research indicates that it is often the case that these 'niche drug provision systems' face many challenges with the quality of new-generation drugs and the implementation of effective pharmacovigilance (PV)<sup>1</sup> systems for the reporting of adverse drug reactions. The lack of resource efficiency in adverse drug reaction reporting within the sub-Saharan context is also a growing concern.

### OPSOMMING

Sedert 2010 het farmaseutiese organisasies deur middel van die *UN Medicine Patent Pool* medisyne patente vrygestel vir lae- en middelinkomste lande. Hierdie inisiatief laat toe dat enige farmaseutiese vervaardiger die patente kan gebruik om medisyne te vervaardig; sodoende word die koste en vervaardigingstyd verminder. Aangesien 'n aantal verskillende vervaardigers, waarvan sommige nie goed gevestigde kwaliteit stelsels het nie, kan deelneem, moet daar goeie 'pharmacovigilance' (PV) toegepas word. Navorsing dui egter daarop dat dit dikwels die geval is dat hierdie plaaslike medisyne vervaardigers baie uitdagings ervaar in verband met medisyne voorsiening wat weer effektiewe PV-stelsels impliseer. Die gebrek aan menslike hulpbronne vir die monitoring van negatiewe reaksies op die medisyne in hierdie lande is ook 'n groeiende probleem.

## 1 INTRODUCTION

In the contemporary landscape it is evident that there has been a significant shift in health care trends around the world that calls for innovative drug manufacturing, distribution, and surveillance monitoring. According to Rohrbach [1], the growing demand for healthcare – combined with the switch in focus from treatment to prevention – has placed pharmaceutical companies under pressure from governments and consumers to reduce their prices and improve the value of their therapies. However, other stakeholders, such as the World Health Organization, also contribute to this pressure. The epidemic of communicable diseases in low- and middle-income countries adds to the pressure that pharmaceutical companies experience from stakeholders to ensure an affordable drug supply. According to the World Health Organization, in 2016 36.7 million people were living with

<sup>1</sup> In this article, 'PV' means 'pharmacovigilance' which refers to the science and application of the detection, assessment, and monitoring of adverse drug reactions after drugs have been licensed for use.

HIV/AIDS, the majority of whom lived in low-middle income countries [2]. These factors, combined with strict drug patent laws, make the affordable supply of drugs in these countries problematic [3].

Thus in 2010 the UNITAID medicine patent pool (MPP)<sup>2</sup> was established to improve access to the treatment of HIV, tuberculosis (TB), and hepatitis C by allowing access to specific drug patents [4], [5]. This innovation has played a significant role in addressing the HIV/AIDS epidemic from the perspective of access to medicine, as between 2005 and 2016 the proportion of patients receiving treatment increased from 6.9% to 53% globally [2]. However, the MPP has given rise to other challenges [6]. As multiple drug manufacturers are allowed to access the drug patents, quality monitoring in these settings has to be very well-established. Such challenges are often attributed to inadequate local drug manufacturing and distribution systems [6].

However, when aiming to address specific challenges brought about by an intervention, as is the case with those arising from the MPP allowing any drug manufacturers access to patents, the context within which such a system exists has also to be considered. As mentioned earlier, the MPP only allows access to patents in low- and middle-income countries, which often have only limited resources. One example of limited resources in the sub-Saharan African region is the deficit of 24.8 million doctors and nurses, resulting in 2.3 healthcare workers per 1000 people in Africa. This is 90% less than in the United States of America, where there are 24.8 healthcare workers per 1000 people [7]. In addition to the limited human resources in these countries, funding and opportunities for research and development are also limited [8]. Thus, when considering the challenges that arise through the implementation of the MPP, the context of limited resources should also be considered.

These challenges in drug manufacturing and distribution in the context of resource-limited settings call for an effective, well-established drug monitoring and pharmacovigilance (PV)<sup>3</sup> system to assist in improving patient safety. In order to develop such a PV system that will support, facilitate, and improve additional challenges brought on by inadequate drug manufacturing and distribution, the challenges need to be identified and understood to ensure that such a PV system overcomes them and does not give rise to any additional ones. It is also recognised that the current PV systems do not adequately support the unique MPP practices. This highlights the need for a PV system to support the unique needs of drug monitoring in such a setting, and to provide evidence that warrants the deployment of a PV system to support effective drug monitoring. In order to develop the characteristics of such a 'niche PV system'<sup>4</sup>, a requirement specification will have to be developed. This requirement specification will be based partly on the insights gained from evaluating the challenges and incorporating best practices, current PV requirements, and the ability of the PV system to function in such a setting. A niche PV system can then be designed either by transforming the traditional PV system or by transitioning to a new PV system using the developed requirement specification.

This paper, however, will focus on the challenges posed by drug manufacturing and distribution systems within resource-limited settings, which will be incorporated into the requirement specification for PV systems for such a setting. These challenges will be identified by conducting a systematic review, after which they will be arranged into a challenges landscape to understand the system perspective. Due to the high prevalence of HIV in South Africa, this research inquiry will consider challenges that arise with the roll-out of antiretrovirals (ARVs) [2].

## **2 CONTEXTUALISATION: MPP DRUG SAFETY, MANUFACTURING, AND DISTRIBUTION IN RESOURCE-LIMITED SETTINGS**

Due to the growing number of HIV/AIDS patients without treatment in low- and middle-income countries, it was evident that an innovative way to provide antiretroviral treatment (ART) had to be

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<sup>2</sup> MPP is an initiative which allows any manufacturer to access the available patents and manufacture drugs; thereby aiming to decreasing lead time and costs associated with these drugs.

<sup>3</sup> 'Pharmacovigilance' is defined as the science and application of the detection, assessment, and monitoring of adverse drug reactions after drugs have been licensed for use.

<sup>4</sup> In this research inquiry, 'niche PV system' refers to a PV system that is designed for a specific population, implying a specific region and a specific drug. Such a PV system will most likely operate and be managed differently from 'traditional' PV systems.

implemented [2], [3]. One of the reasons that very few HIV/AIDS patients did not receive treatment was the high prices for treatment caused by the patent system, in which a company had the monopoly over a particular drug. ARVs also have to be taken in combination with other drugs, each with their own patent; and this also resulted in very high prices [3].

Thus, in 2010 the MPP was established by UNITAID to increase access to treatments for specific communicable diseases such as HIV, hepatitis C, and TB in low- and middle-income countries through sharing technologies and patents [4]. A patent pool is defined as a collaboration between patent holders and other third parties, where licences are offered for use in exchange for a fixed price or royalties. The implementation of a medicine patent pool makes the production and distribution of drugs accessible to a broader population at a faster rate and at more affordable prices [3]. The WHO assist the MPP by prioritising the medicines that were required, and patent holders voluntarily agreed to license their medicines to the MPP, which in turn issued generic pharmaceutical companies with licence rights to manufacture these medicines.

The implementation of MPP has many advantages, such as facilitating competition, improving low-cost manufacturing, and encouraging research and development (R&D) [3], [9]-[11]. Through the implementation of the MPP, competition is facilitated because multiple drug manufacturing companies can access the same patents. As competition between manufacturers increases, drug prices drop, making drugs more affordable [9]. Through the MPP, low-cost manufacturing companies are also able to approach the patent pool to negotiate licensing agreements to create generic versions of these drugs [3]. As mentioned earlier, antiretroviral drugs need to be taken in combination with other drugs in order to be effective [3]. However, the patent pool encourages R&D and innovation for the treatment of HIV/AIDS, as the patents for the drugs are accessible and can be used for new fixed-dosage combinations [3], [10]. The manufacturing companies are given the flexibility to develop new and appropriate formulations and fixed-dosage combinations to meet the specific needs of patients. Often the drugs are not adapted for use in developing countries – as in the case of paediatric treatments, as virtually no children are affected by HIV/AIDS in developed countries [9]-[11].

However, certain challenges arise when considering the provision of access to medicine through the MPP, such as local manufacturing, distribution, R&D, sub-standard medicines, and other regulatory issues [6]. The patents are available to any drug manufacturing companies in low- and middle-income countries that wish to make use of them; and although the manufacturers need to meet certain quality standards, it is often difficult to monitor the quality process of these drugs. Research found that, although the MPP does not directly cause any difficulties, the drug manufacturing and distribution system in these settings, made possible through the MPP, produces numerous challenges [12], [8].

In section 3, the different challenges that arise due to inadequate manufacturing and distribution systems in resource-limited settings will be identified through a systematic review, after which they will be discussed before developing a challenges landscape.

### **3 CHALLENGES POSED BY DRUG MANUFACTURING, DELIVERY, AND RESOURCE-LIMITED SETTINGS**

As previously mentioned, the challenges that arise in the manufacturing and distribution of drugs for which patents are made available through the MPP can be attributed to inadequate drug manufacturing and distribution systems [6], [12]. These challenges affect patient safety, and so need to be addressed to ensure that the necessary monitoring systems are in place. The low- and middle-income countries that access the MPP also often have limited resources, which further complicates the challenges [7].

In this section, the aim is to identify the challenges arising from drug manufacturing and distribution systems in resource-limited settings in developing countries. Once these challenges have been identified through a systematic review, a challenges landscape can be developed to indicate the system perspective, which will contribute to the development of the requirement specification for a PV system in these settings.

First the approach to, and the results of, the systematic review will be given, after which the different challenges will be defined.

### 3.1 Approach

Due to the great extent of the available literature on drug manufacturing and distribution, a systematic review was conducted to limit the review and ensure that a significant amount of research into the challenges in this landscape could be included. The academic database Scopus—the largest abstract and citation database of peer-reviewed literature<sup>5</sup>—was used to conduct the primary search protocol. In addition, since the use of keywords in a search protocol is most effective in Scopus, and other databases often deliver irrelevant documents when using this search technique, Scopus was deemed a suitable platform for this research inquiry. However, given the focus on healthcare environments, databases such as PubMed were used for informal search methods, and serendipitous findings were included in the research. Using Scopus, a total of 1870 relevant articles were found using specific key words and phrases (Table 1). In order to find the most relevant documents, a set of different criteria points were included in the search protocol. These criteria points included only documents from 2010 and onwards, as the MPP was only introduced in 2010. Furthermore, documents that were not originally published in English but had been translated, and any duplicate documents, were excluded. The remaining documents' titles and abstracts were then screened for relevance. Documents concerned with relevant topics, such as the challenges posed by drug manufacturing or distribution systems or settings with limited resources regarding HIV/AIDS, were included in the final set. In the end, a total of 41 relevant documents were found from Scopus and seven from PubMed. These were reviewed and used to identify the challenges that are experienced in the context of drug manufacturing and distribution systems in resource-limited settings.

The process that was followed to limit the number of documents can be found in Figure 1.

**Table 1: List of search terms used in systematic review**

Index	Search terms	Number of articles	Number after 2010
1	Drug Manufacturing	480	257
2	Drug Manufacturing & Challenges	45	31
3	Drug Manufacturing & HIV	4	1
4	Drug Manufacturing & Developing Countries	16	8
5	Drug Manufacturing & HIV & Challenges	1	1
6	Drug Manufacturing & Challenges & Developing Countries	3	1
7	Drug Manufacturing & Quality	188	102
9	Drug Distributions & Challenges & HIV	232	147
10	Drug Distributions & Challenges & Developing Countries	14	7
11	Drug Resistance & HIV & Developing Countries	352	189
12	Counterfeit drugs & Developing Countries	126	84
13	Resource Limited Settings & Challenges & HIV	337	257
14	Resource Limited Settings & Challenges & developing countries	144	123
15	Patient safety & HIV & Developing Countries	24	17
16	Drug Packaging & Challenges & HIV	10	5
17	Drug Packaging & Challenges & Developing Countries	9	8
18	Adverse Drug Reactions & Drug Manufacturing	58	29
19	Adverse Drug Reactions & HIV & Developing countries	84	64

<sup>5</sup> <https://www.elsevier.com/solutions/scopus>

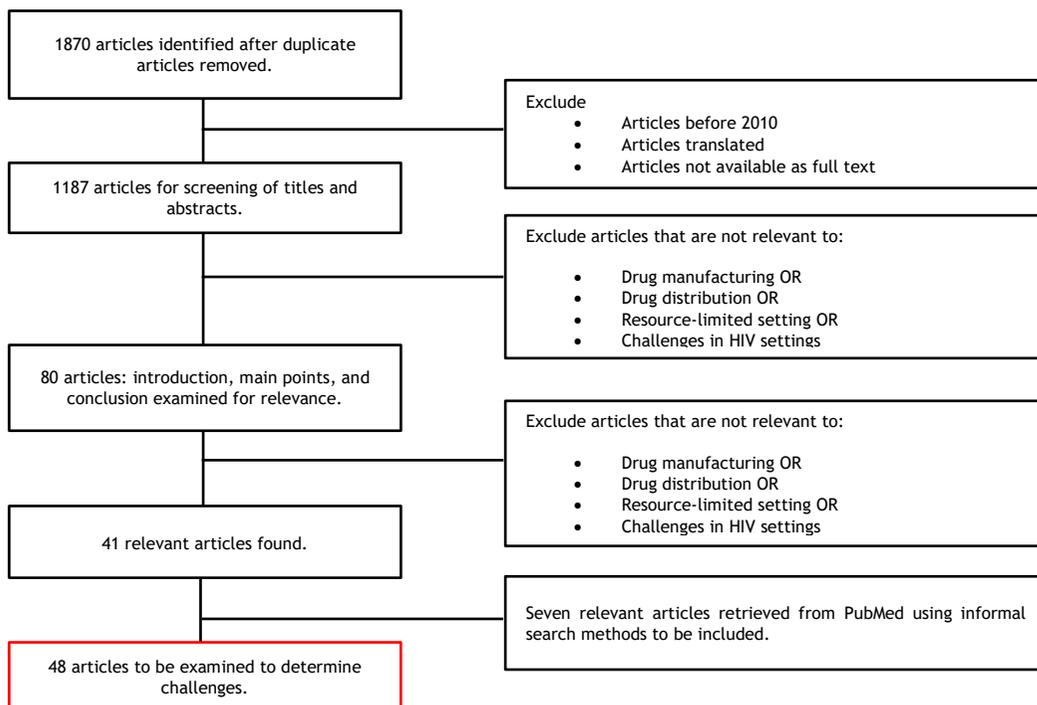


Figure 1: Process of systematic review

### 3.2 Results

Once the systematic review had been completed, the different challenges posed by inadequate drug manufacturing and distribution systems, and the challenges posed by limited resources, could be identified and listed. From the literature the following 19 factors were identified:

- Drug dosages
- Labelling & packaging
- Specialised drugs
- Traditional medicines
- Paediatric drugs
- Drug resistance
- Drug quality
- Counterfeit drugs
- Substandard drugs
- Record-keeping
- Adverse drug reactions (ADR)
- Drug-drug interactions
- Drug adherence
- Drug supply
- Drug shortages
- Drug stock-outs
- Late ART initiation
- Lack of safety reporting
- Integrity of system

Table 2: Overview of occurrences in systematic review

Occurrences of challenges in systematic review																			
Date	Drug Manufacturing				Combination of distribution and RLS			Combination of manufacturing, distribution and RLS						RLS					
	Dosages	Paediatric drugs	Specialised drugs	Traditional medicine	Labelling	Drug supply	Drug stock-outs	Drug shortages	ADR	Drug adherence	Quality	Counterfeit drugs	Drug-drug interactions	Substandard drugs	Drug resistance	Lack of safety reporting	Record-keeping	Late ART Initiation	Integrity of system
2010				XX			X			X	XX			X		XX	XX	X	X
2011	X	X	X			XX	X	X	XX	XX	X				X	X		XX	
2012									XX	X		X							
2013	X				X	X	X		X	X	X	X	XX	X	XX				
2014						X			XXX	XXX	X	X	X	X		X	X	X	X
2015			X						X	X	X		X	X					
2016	X	X	X					X	XXXX	X	X		X			X	X		
2017		X		X	X						X	X						X	
<b>Total</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>2</b>	<b>4</b>	<b>3</b>	<b>2</b>	<b>13</b>	<b>9</b>	<b>8</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>3</b>	<b>5</b>	<b>5</b>	<b>4</b>	<b>2</b>

Each X represents a document

From the data provided in Table 2, a number of trends seem to emerge, as some challenges are only mentioned in more recent years. For example, labelling, specialised drugs, drug-to-drug interactions, and lack of reporting have appeared in the more recent literature, while challenges

such as drug shortages and drug resistance have not appeared in the literature in recent years. From Table 2 it can also be seen that certain challenges have occurred more constantly over the last eight years, such as ADR and quality challenges.

### **3.3 Defining challenges**

The 19 factors that were identified in the systematic review have a specific impact on the pharmaceutical and healthcare systems. These challenges are defined and explained in the next sub-section.

#### **3.3.1 Adverse drug reactions**

According to the WHO, an ADR is defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” [13]. ADRs can affect the treatment process and have negative effects on patients’ quality of life, especially for HIV-infected patients on ART. Serious ADR often causes patients to stop taking drugs, leading to a lack of drug adherence or to treatment failure, which negatively impacts patients and society. ADRs are also often a cause of re-admission to a hospital, aggravating the health care burden in resource-limited settings [14]-[19]. It has also been shown that ADRs have been found to be preventable, justifying the need to improve pharmacovigilance. The early detection of ADRs is also pivotal when ensuring the sustainability and optimisation of a treatment process. However, it has been reported that detection, especially in paediatric treatments, is difficult [20]. Furthermore, through the MPP, multiple drug manufacturers are able to produce generic drugs and new fixed-dosage combinations, making it critical that ADRs in HIV patients are monitored carefully [14], [18], [19].

#### **3.3.2 Drug adherence**

‘Drug adherence’ refers to patients keeping to the recommendations made for the dosage, timing, and frequency of taking their medication. With regard to ART, it is said that 95% drug adherence is required to ensure that patients do not develop resistance or suffer from treatment failure [21]. From the literature consulted, it has been determined that non-adherence in ART is caused by a range of different factors; but one of the main causes is ADR [17], [18], [22]. However, studies in developing countries have also indicated that other factors contribute to non-adherence, such as dissatisfaction with the healthcare system, perceived stigmas, distance to ART clinics, limited social support, poor record-keeping, the attitude of healthcare workers, and certain personal factors [23], [17], [21]. Studies do indicate, however, that adherence can be improved with peer counselling and education [24].

#### **3.3.3 Quality**

Ensuring that the drugs that patients take are safe and effective is one of the priorities of the pharmaceutical industry, and it needs to be continuously addressed throughout the process. Many different aspects, such as good manufacturing practices, quality monitoring, and drug plant characteristics contribute to low-quality drugs. It has been found that, in low income countries, the quality of drugs is often inconsistent; thus proper quality control should be assessed more often, especially when new drug manufacturers are used [25]-[27]. Another aspect to consider when addressing drug quality is the production of generic drugs, which is promoted through the MPP. Generic drug manufacturing and the production of fixed-dosage combinations challenge the existing system, as the different areas of responsibility are misunderstood [28], [23].

#### **3.3.4 Lack of reporting**

Limited human resources in developing countries contribute to the lack of reporting of ADRs, especially in public HIV healthcare systems. Most low- and middle-income countries have inadequate legislation for mandatory reporting by health care professionals [29], [30], [31]. Furthermore, it has been found that the severity and preventability of ADRs are often under-reported in developing countries, possibly due to inadequate healthcare resources and knowledge among healthcare workers in these regions [14].

#### **3.3.5 Record-keeping**

Medical health records are essential to health care providers, as they contain specific information about a patient, such as their unique patient identifiers and medical history. Medical health records contain vital information about a patient’s health, and are needed for their current and future treatment. Health care providers are required to write up health records so that the information is available when the patient returns to a health care facility [32], [33]. However, it is often the case

in developing countries that effective record-keeping is a challenge [31], [34]. Healthcare providers mention that patients' records are often lost, resulting in the loss of all previous data, and sometimes even leading to certain medical procedures being repeated [21]. This therefore underpins the need for effective record-keeping systems, such as electronic health records.

### **3.3.6 Counterfeit drugs**

The WHO describes counterfeit or falsified drugs as “medical products that deliberately/ fraudulently misrepresent their identity, composition or source” [35]. The WHO also states that counterfeit drugs can be branded or generic drugs that contain the incorrect ingredients, or none at all, or inadequate amounts of active ingredients, or that are falsely packaged [36]. The health of patients who receive counterfeit drugs is threatened, as they are at risk of developing ADR or drug resistance [23], [27], [28], [37]. Counterfeit drugs are often a concern in areas where there is a shortage of drugs, or drug manufacturing and distribution systems are not registered [23], [38].

### **3.3.7 Drug-drug Interactions**

The interaction between ARVs and other drugs is often harmful to a patient's treatment procedure. ARVs are often co-administered with antitubercular medication; however, this often leads to a higher frequency of drug-induced liver incidents and peripheral neuropathy. Thus TB/HIV co-infected patients' treatment should be managed more carefully. ‘Drug-drug interaction’ is defined as a change in the effect of the drug when it is taken together with another drug, and it can often lead to ADR [39]. The use of traditional medicines has also given rise to challenges in drug-drug interactions [23].

### **3.3.8 Drug supply**

In developing countries, drug supply has often been a concern, especially for illnesses such as TB and HIV/AIDS, whose treatment requires a strict regime to be effective. Furthermore, when limited amounts of ART are available, ethical issues often arise about how the medication should be prioritised for different patients [23]. Delays in drug delivery in resource-limited settings are often caused by poor infrastructure such as poor roads and by financial burdens such as a lack of funding for fuel [37], [40]. The challenges posed by poor drug supply involve all aspects of the supply chain, from ordering systems to the storage and distribution of drugs. Case studies on weak ARV supplies in South Africa found that they were often caused by poor communication between provincial districts and facilities or between the consumer and the facilities. Studies have shown that supply systems that rely on consumer ordering affect shortages [41].

### **3.3.9 Late ART initiation**

From the literature it has become evident that the need to ensure that people start their treatment during the early phases of the disease is just as important as ensuring that patients receive treatment [42]. Although there is no clear definition of just when it is ‘late’ for a patient to start ART, it can be deduced that it is when a patient's CD4 count is very low ( $CD4 < 50$  cells/ $\mu$ L). Patients who initiate late ART have a higher risk of opportunistic infections than patients who start treatment at a higher CD4 count, with TB being the most common illness [43], [44]. From previous studies, the causes of late ART initiation can be grouped into health system-related issues, socio-economic obstacles, or inappropriate treatment criteria [44].

### **3.3.10 Substandard drugs**

The WHO defines substandard drugs as “authorized medical products that fail to meet either their quality standards or specifications, or both” [35]. A drug is thus regarded as a substandard drug if it contains too many or too few active ingredients in comparison with the formulation specifications. However, there have been substandard drugs that were toxic in nature or that contained fatal levels of toxic ingredients. Substandard drugs are often found in poorer settings with manufacturing and distribution systems that use unqualified personnel and inadequate control systems. Substandard drugs are more frequently found, and pose a greater threat to patients than counterfeit drugs [27], [36].

### **3.3.11 Dosages**

Taking the correct dosage when on ART is important, since taking an incorrect dosage leads to there being an inadequate amount of the drugs to fight the virus. Often, when tablets are split, asymmetry results in an unproportioned dosage of the ARV drugs. Furthermore, it cannot be assumed that the ingredients are evenly distributed in a tablet; thus pill splitting is not recommended [45].

### **3.3.12 Drug resistance**

Drug resistance is when the response to a drug in a susceptible parasite population decreases significantly [46]. According to studies by the WHO, it was found that in 2010 the prevalence of HIV drug resistance for patients starting treatment was 6.8% for any drug, and that the treatment of these patients was more likely to fail [47], [48]. Drug resistance leads to further challenges relating not only to the patient's own future treatment, but also to the whole community [25].

### **3.3.13 Drug stock-outs**

The WHO defines a drug stock-out as the total absence of a medication that has been identified as essential at the point of service delivery [49]. Drug stock-outs are often the result of poor infrastructure and insufficient human resources [40], [50]. Although alternative ARTs are often provided in the case of a stock-out, it still poses the threat of drug resistance, as it might cause suboptimal drug levels [34]. It has been reported that one-third of countries worldwide struggle with drug stock-outs, thus increasing the risk of treatment failure and failed drug adherence [30], [34], [51]. To ensure that stock-outs do not occur, it is critical that ART programme planning and rational forecasting processes are in place [30].

### **3.3.14 Paediatric drugs**

The need for paediatric antiretroviral drugs is much higher in low- to middle-income countries, as developed countries have significantly reduced the mother-to-infant HIV rate. Furthermore, the use of adult ART for children is seen as ineffective, as children absorb and metabolise drugs differently than do adults. Through the MPP, drug manufacturers in developing countries can develop innovative fixed-dosage combinations specifically for paediatric use. However, when developing paediatric drugs, the palatability, taste, size, dosages, formulation, and ease of handling or administration of the drugs should be considered [45], [52].

### **3.3.15 Specialised drugs**

In developing countries, certain specialised drugs are manufactured to specific contextual criteria. Two examples of such drugs that occur in the HIV treatment context are paediatric antiretrovirals and the use of traditional medicines. This is often the case in countries that are part of the MPP, as the patents often only cater for a developed country's needs [53], [45].

### **3.3.16 Traditional medicines**

Many cultural and social differences that further complicate HIV/AIDS treatment in developing countries need to be considered, one being the increasing production and use of traditional medicines [54]. The increased production of these medicines raises issues of quality control, although intercultural standards are being developed for traditional medicines. Aspects to consider in relation to quality control are the use of raw materials, the knowledge of the manufacturers, and the lack of general safety studies [55]-[57].

### **3.3.17 Drug shortages**

A drug shortage is defined by the WHO as the insufficient supply of medication or health products to meet the public's and patients' needs [49]. The drugs that are often affected by shortages are produced by smaller generic companies with little redundant capacity, which complicates the situation with production problems [58]. Previous case studies showed that patients who were on a waiting list for ART often died due to drug shortages. However, drug shortages can be prevented if there are sufficient resources to inspect and approve new drugs and ensure the quality of drugs. It has also been predicted that reducing the number of reviews and speeding up inspections would help to avoid shortages [59].

### **3.3.18 Integrity of system**

The support, integrity, and confidentiality of health care workers has been seen to have an impact on ART. From the literature it has been found that HIV patients' distrust of and dissatisfaction with the healthcare system can lead to serious problems such as late treatment initiation or poor drug adherence, which often result in drug resistance or treatment failure. Healthcare workers who are supportive will motivate patients to take their ARVs, and educate them about the consequences and benefits of keeping to the treatment programme [21], [44],[60]. A case study [44] revealed that HIV patients often do not seek treatment, as they know that the healthcare staff often discuss their status – which is a very sensitive topic – in public. The compassion and support of healthcare workers are important in ensuring that patients follow through with their treatment [25].

### 3.3.19 Labelling

Mislabelling drugs can have a severe impact on a patient's safety, and can be more harmful for them. According to the WHO, labelling on drugs needs to contain the names and amount of the active ingredients, the batch number from the manufacturer, the expiry date, the name and address of the manufacturer, any storage instructions, and directions for use. It is particularly important that the directions and guidelines for use are clearly indicated [61].

## 4 CHALLENGES LANDSCAPE

As previously mentioned, the challenges that were identified in section 3 were found to relate to one another and to have an impact on one another. It was also established that challenges could have (possibly different) impacts on the various parts of the pharmaceutical value chain. Thus, an overview of the 'challenges landscape' is developed here to gain a holistic view of the challenges that face the drug manufacturing and distribution systems in relation to the provision of drug patents through the MPP. The challenges landscape will serve as a guide to determining any shortcomings in the traditional PV system by developing a requirement specification for a (niche) PV system that will support effective and efficient drug surveillance and monitoring. However, the development of the requirement specification falls outside of the scope of this paper; the key focus of this paper is, as mentioned earlier, to develop a challenges landscape to understand the system perspective in these settings.

The pharmaceutical value chain framework used for the purpose of this study has four sections: supply, distribution, product, and health system [62]. The 'supply' section is then sub-divided into 'drug development' and 'manufacturing', while the 'health system' section is split into 'patient usage' and 'monitoring systems' [62].

The challenges landscape, as discussed in the sections that follow, is discussed from three perspectives: firstly, the relationships between the various challenges are considered and presented in a relationship diagram; secondly, the relationship diagram, the pharmaceutical value chain framework, and the various challenges are amalgamated and presented in a schematic representation of the challenges landscape; and thirdly, the linkages and groupings presented in the schematic representation of the challenges landscape are elaborated on.

### 4.1 Relationship diagram & schematic representation of the challenges landscape

In Figure 2 the respective relationships between the challenges are indicated. These relationships were not necessarily explicitly mentioned in the literature, but after synthesising the information gathered through the systematic literature review, certain correlations and relationships between the different challenges could be identified. The relationships indicated in Figure 2 are grouped so as to indicate the impact a relationship has on a specific section of the pharmaceutical value chain. These sections of the value chain are distinguished in the key provided in Figure 2. In the case where a relationship has an impact on more than one section, both are indicated. The relationship diagram was used as an aid to create the challenges landscape. Schematic representation of the challenges landscape

Using the relationship diagram in section 4.1 and the information from section 3, a challenges landscape (Figure 3) was developed to indicate the inter-relationships and impacts between the different challenges, and their relationships with the different stages of the pharmaceutical value chain.

As seen in the schematic representation, the pharmaceutical chain is subdivided into four sections: supply, distribution, product, and health system. The challenges are in three main groups, referred to as A1-A3. They are formed when considering the systematic review and the causes of the challenges – namely, drug manufacturing and distribution in resource-limited settings. A1 refers to challenges due to inadequate manufacturing and distribution systems; A2 to challenges due to quality issues in drug manufacturing and distribution; and A3 to challenges due to limited resources. These challenges are grouped in subsections within these main groups; these sub-groupings, C1-C8, are discussed in section 4.2.

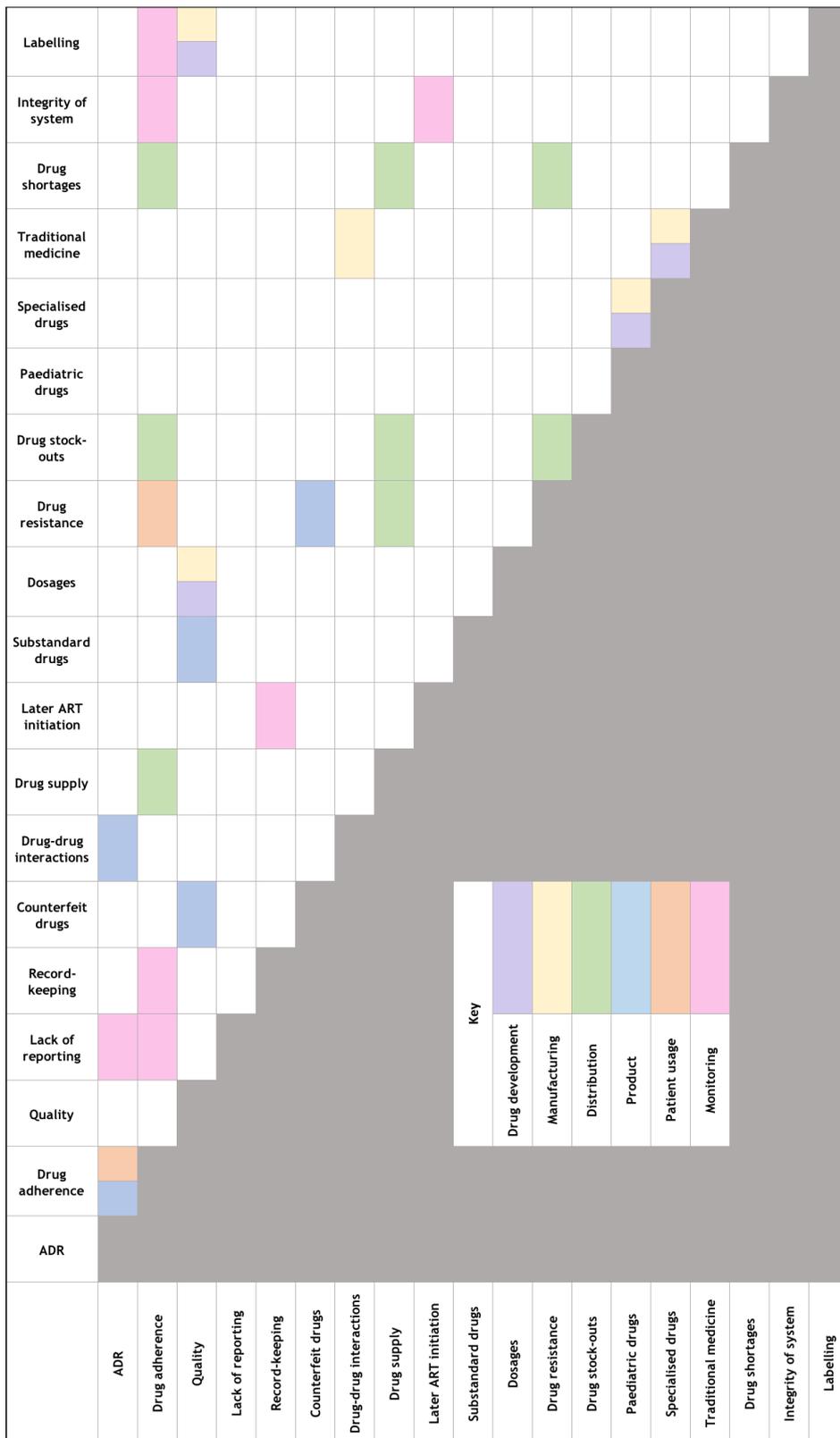


Figure 2: Relationship diagram (see online version for colour)

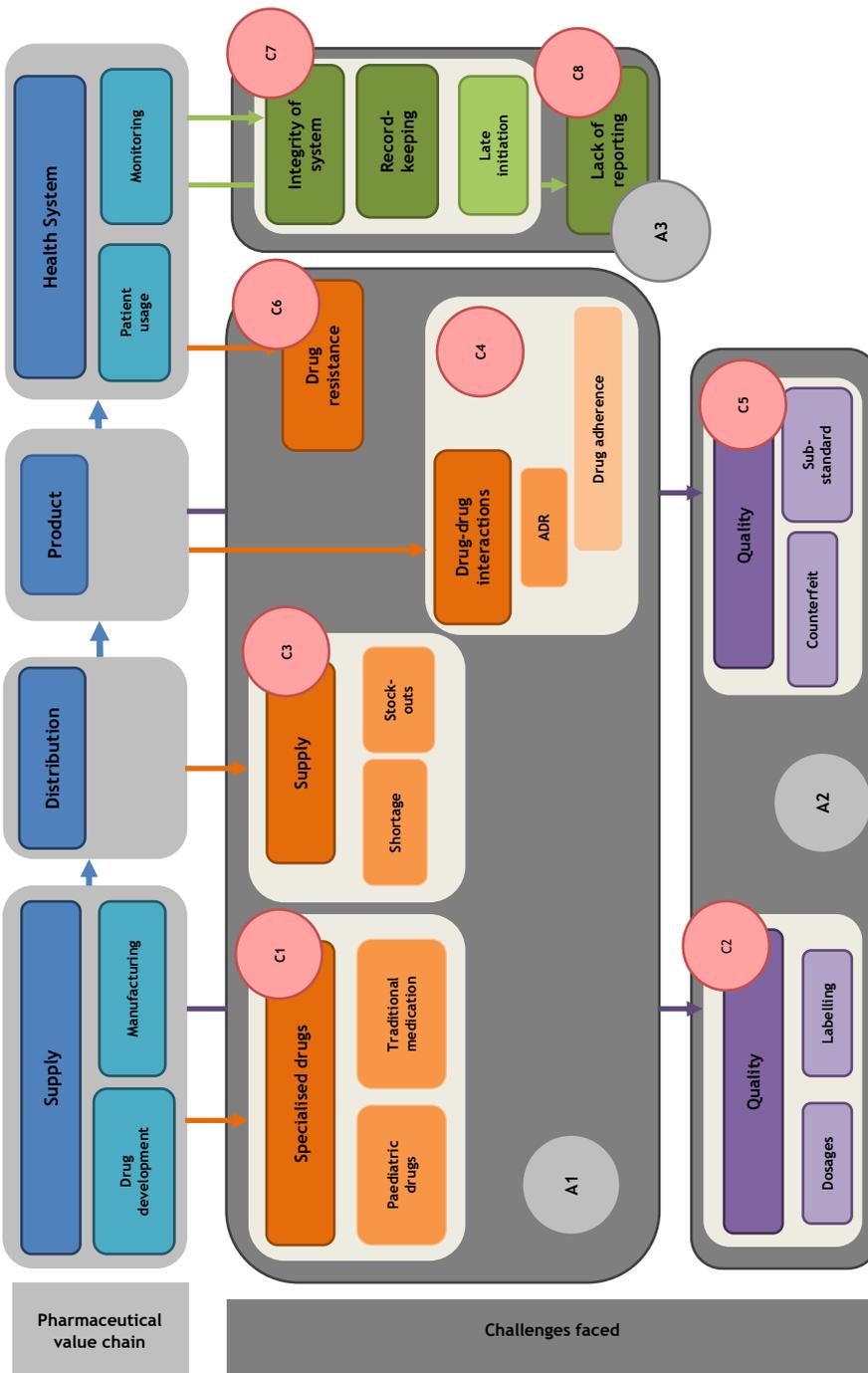


Figure 3: Challenges landscape (see online version for colour)

#### 4.2 Links and groupings

As mentioned earlier, the different challenges have certain correlations, impacts, and/or relationships on or with each other, either directly or indirectly, which are illustrated by the challenges landscape in section 4.1. The explanation of the different groupings and relationships in the challenges landscape is provided in Table 3. It should be noted that the groupings and links between the different challenges were created with reference to the literature that was found through the systematic review and provided in section 3.

**Table 3: Explanation of groupings of different challenges**

Code	Value Chain	Grouping	Explanation
C1	Drug development and manufacturing	Specialised drugs, paediatric drugs, traditional medicines	In low- and middle-income countries, the development and manufacturing of drugs often requires the creation of drugs for specific needs of patients, referred to as 'specialised' drugs. In the case of HIV, the two specialised drugs that are most often found are paediatric drugs and traditional medicines [53], [45]. These challenges mostly appear in the phases of drug development and manufacturing. Furthermore, it is seen that traditional medicines often have an impact on drug-drug interactions [23].
C2	Drug development and manufacturing	Quality, dosages, labelling	The identified quality challenges have been shown to have an impact on the supply side of the value chain. Drug manufacturing companies have to have quality systems in place to ensure that the drugs they manufacture are safe and effective, and will not harm patients [26], [27]. Inadequate quality systems in drug manufacturing companies further complicate challenges such as drug dosage and labelling. If drug manufacturing companies do not have quality systems in place, the drugs dosages are often not adequate, as the ingredients are not distributed evenly [45]. The labels are often also incorrect. These challenges cause further problems with patient safety [61].
C3	Distribution	Drug supply, drug shortages, drug stock-outs	In the drug distribution part of the value chain, drug supply in low- and middle-income countries is one of the major concerns that is further affected by limited resources in these settings. As mentioned, many factors affect drug supply, from poor infrastructure to factors in the supply chain such as ordering systems [41]. The problems in drug supply create difficulties such as drug shortages and drug stock-outs. These lead to problems with patient safety, since shortages and stock-outs often are the causes of drug resistance in patients and poor adherence [34].
C4	Product, patient usage	Drug-drug interactions, ADR, drug adherence	Of the challenges that were identified, drug-drug interaction is one that arises in the final product stage of the value chain. As mentioned, ARVs often have to be taken in combination with other drugs, which can lead to negative drug-drug interactions. It has also been found that traditional medicines, which are often used in low- and middle-income countries, have an effect on drug-drug interactions [23]. Drug-drug interactions often also cause serious side effects and ADRs [39]. As previously mentioned, ADRs often have an effect on a patient's treatment process, as serious ADRs can impact a patient's adherence to the treatment, since they often stop taking their medications due to ADRs [21]. This inevitably affects not just the patient but the community as a whole. Drug adherence implicates the value chain in both the final product stage and the patient usage stage.
C5	Product	Quality, counterfeit drugs, sub-standard drugs	The quality of the final product is reduced by ineffective manufacturing and distributions systems [27], [28]. Drugs of inauspicious quality often lead to counterfeit drugs or sub-standard drugs. These challenges are mostly caused by a lack of quality in the drug supply process, and can seriously affect patient safety. Furthermore, counterfeit drugs often lead to serious ADR or drug resistance [23], [27], [28], [37].
C6	Patient usage	Drug resistance	Drug resistance is one of the challenges in the HIV setting that is associated with patient usage. Although drug resistance is not grouped together with other challenges, many factors impact on and lead to drug resistance. From the identified challenges, the biggest contributors to drug resistance are drug delivery, shortages, stock-outs, and poor drug adherence [34], [42]. Furthermore, drug resistance is complicated by inadequate drug monitoring systems, such as the low integrity of a health system and poor record-keeping [21], [44].
C7	Monitoring	Integrity of the health system, record-keeping system, late ART initiation	In monitoring – the final stage of the drug value chain – many challenges arise from limited resources. The poor integrity of the health care system and the lack of effective record-keeping are two of the contributing factors for late ART initiation. Late ART initiation can be very detrimental to patient care, and often leads to unnecessary deaths. Furthermore, the lack of effective record-keeping and dissatisfaction with the health care system affects drug adherence, which again leads to drug resistance [44].
C8	Monitoring	Lack of reporting	The lack of reporting during ART is one of the major challenges in resource-limited settings during the monitoring stage of the value chain. As mentioned, preventable ADRs have often been found to be under-reported, leading to further complications such as poor drug adherence and drug resistance [14].

### 4.3 The need to investigate the development of a niche PV system

Given the challenges landscape discussed above, the three perspectives – the relationships between the various challenges, the schematic representation of the challenges landscape, and the discussion on the linkages and groupings – lead to a comprehensive understanding of and insight into the challenges that arise from drug manufacturing and distribution systems that are related to the MPP

in settings with limited resources. From this challenges landscape, it is evident that there are shortcomings in the current (traditional) PV systems, as the challenges faced in these settings are not considered or incorporated when developing and designing the requirements and characteristics of a traditional PV system [63].

Thus, the challenges landscape highlights the need for an innovative PV system, such as a niche PV system, not only to support, facilitate, and improve the manufacturing and distribution of drugs and to address the challenges faced in these settings, but also to ensure that such a PV system will not create any additional problems or reinforce existing ones. The insights gained from the challenges landscape will assist with the development of a requirement specification for such a niche PV system that will address the current shortcomings in drug surveillance and monitoring in these settings.

## 5 CONCLUSION AND FURTHER RESEARCH

The challenges that arise in the manufacturing and distribution systems of drugs whose patents are made available through the MPP were discussed in this article. The challenges specifically related to developing countries, and challenges faced within the HIV/AIDS setting, were considered. It was determined that these challenges complicate different stages of the pharmaceutical value chain, and thus an innovative PV system is required to address these challenges.

The challenges landscape developed in this paper is a useful tool that indicates the relationships from a system perspective. Furthermore, the challenges landscape and the insights gained from it can be used in combination with other elements that relate to drug surveillance monitoring, such as best practices and current PV characteristics, to develop a requirement specification for an effective PV system in these settings.

In conclusion, this paper highlights the need for an innovative PV system, such as a niche PV system for a specific region and specific drug, to address and possibly eliminate the challenges that are faced in these settings, and to increase the effectiveness and efficiencies of such systems, given their unique characteristics. The insights gained from this paper will be considered when designing a niche PV system by transforming or transitioning from the traditional PV system.

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