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Impact of Regulatory requirements on medicines access in African countries

PIASA member survey results

PIASA
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Table of Contents

1 PIASA Background

The Pharmaceutical Industry Association of SA (PIASA) is a trade association of companies involved in the manufacture and/or marketing of medicines in South Africa. The membership includes a broad representation of foreign multinational pharmaceutical companies and local and generic companies, both large and small. The membership includes South African pharmaceutical companies Adcock Ingram Limited and Sekunjalo/Bioclones (Pty) Ltd, with the rest of the membership being drawn from the long-established Pharmaceutical Manufacturers' Association (PMA) – a total of 18 member companies. The grouping represents >33% of the total private sector pharmaceutical market in South Africa.

2 Objective

The objective of this survey was to determine both the nature and extent of regulatory hurdles experienced by companies in seeking Market Authorisation for medicines in African countries. The target groups for the survey were the PIASA Export working group and the PIASA Regulatory working group. Specific commercial issues were avoided for reasons of Competition Law.

3 Methodology

An online survey was used based on key issues that were provided by the PIASA Export and Regulatory working groups using Survey Monkey (www.surveymonkey.com). Emails were sent to both working groups with a link to the online survey. Reminders were sent to increase the response rate to the survey.

3.1 Survey design

Through the experience of previous PIASA submissions to regulatory authorities in African markets, feedback from members of the PIASA Export and Regulatory working groups and feedback from Prof Eric Buch (Nepad Health Advisor), questions were set up to address key issues.

The survey was also structured with open ended questions to allow respondents to express their views freely as well as provide specific examples of experiences.

4 Results

26 respondents completed the survey from the PIASA Regulatory working group.

7 respondents completed the survey from the PIASA Export working group.

In instances where more than person responded from a particular company, duplicate responses were removed, i.e. to ensure one response per company for a particular question.

4.1 Demographics

The following PIASA companies participated in the survey: Refer to Table 1.

Table 1: companies that participated in the survey

Company	Regulatory	Export
Abbott Laboratories	✓	✓
Adcock Ingram	✓	✓
AHN Pharma	✓	
Alcon Laboratories	✓	✓
AstraZeneca	✓	
Bayer Animal Health	✓	
Bioclones Pty Ltd	✓	
Covidien	✓	
Galderma Laboratories	✓	✓
Janssen-Cilag	✓	✓
Merck	✓	
Merck Serono	✓	✓
MSD	✓	
Novo Nordisk	✓	
Solvay Pharma	✓	

5 Medicines supply to Africa by Region

Many PIASA member companies have started to expand their businesses into Africa. South Africa is well placed to supply medicines into African markets. The survey conducted shows the level of participation of PIASA member companies in the various countries in Africa, as described in Table 2 below.

Table 2: Summary of African regions that PIASA member companies currently operate in

Region	No. of Companies that supply medicines to this region
SADC	14
ECCAS	7
ECOWAS	10
EAC	10

5.1 Number of products supplied to African regions

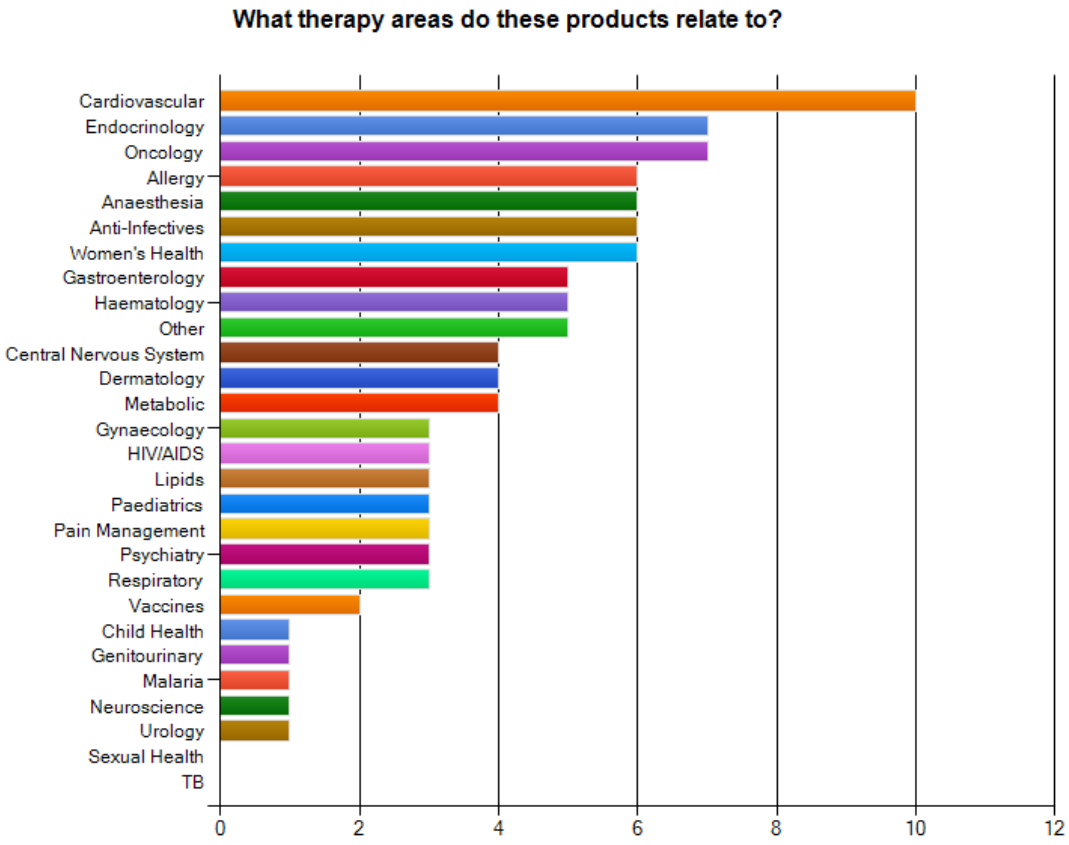
Table 3: Number of product lines supplied by companies by African region

Region	Number of Products Supplied vs. number of Companies				
	1-5	**6-10**	**11-15**	**16-20**	**>20**
SADC	3	3	1	3	5
ECCAS	1	3	1	2	2
ECOWAS	0	3	0	1	3
EAC	0	3	1	2	4

5.2 Therapy areas covered

PIASA member companies cover a broad spectrum of therapeutic areas including diseases where the prevalence in Africa is high (viz. anti-infectives, HIV/AIDS) and specialized diseases e.g. oncology.

Figure 1: therapy areas covered by PIASA members



5.3 Generic Equivalents

Generic equivalent medicines are available for **73.7 %** of medicines supplied in the following therapeutic areas. It should be noted that some PIASA member companies also supply multisource products (i.e. generics).

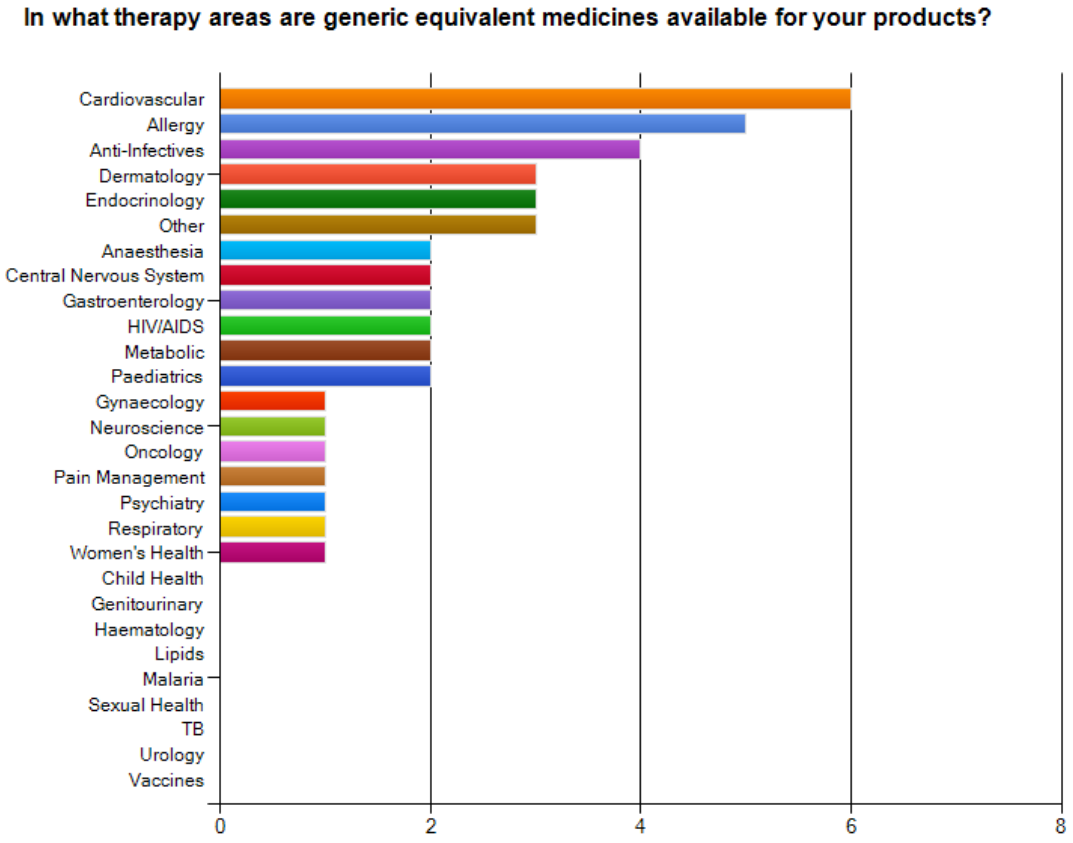


Figure 2: Generic equivalents available by therapeutic area

5.4 Country Specific Requirements

Over recent years, pharmaceutical companies globally have rationalized manufacturing sites to reduce costs. This has resulted in medicines being supplied from centres of excellence around the world. This increases the complexity in managing country specific packaging where the market size is small. More and more African countries are introducing country specific requirements, which make market access difficult. Country specific labeling[1] requirements do not support the principles of harmonisation.

[1] Includes Scheduling status and registration numbers printed on the medicine packaging

Country specific labeling requirements increase the cost of medicines to specific African countries and in some cases companies cease to supply medicines to these countries. **89.5%** of respondents stated that country specific labeling requirements are problematic to implement.

Table 4: Respondents view of country specific requirements impact on registration and access to medicines

Region*(no. of companies)	Yes (%)	No (%)	No Opinion (%)
EAC (10)	100	0	0
ECCAS (6)	100	0	0
ECOWAS (7)	100	0	0
SADC (14)	92.9	7.1	0

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory Group)

There was strong feedback regarding the feasibility of implementing country specific labeling. Comments included the following:

'The volume purchased by some of these countries does not justify the cost of implementing a country specific label.'

'Volumes of product do not justify developing labels for each country. Logistics becomes very complex.'

'Increases costs.'

'Need to be able to use one label for all countries and find a more novel way to include country specific requirements on these labels.'

'Quantities sold in these countries do not justify the production of a country specific pack.'

5.5 Registration timelines and requirements

The figure below, (Figure 3), illustrates the responses to companies' experience in timelines to register medicines in African countries.

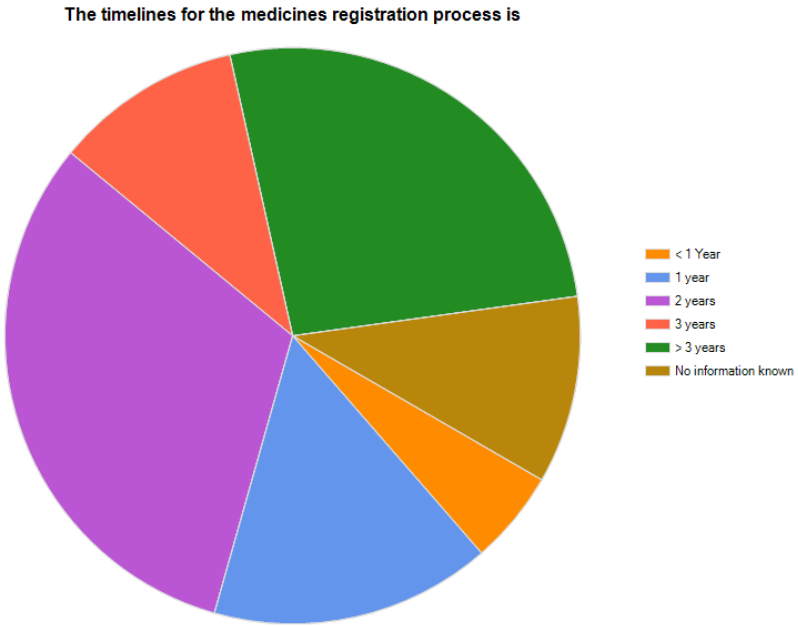


Figure 3: Overall timelines for registration process

Table 5: timelines for registration by economic region

Region*(no. of companies)	<1 year (%)	1 year (%)	2 years (%)	3 years (%)	>3 years (%)
EAC (11)	9.1	9.1	45.5	9.1	27.3
ECCAS (8)	12.5	0	50	12.5	25
ECOWAS (8)	12.5	0	50	12.5	25
SADC (15)	6.7	20	40	0	26.7

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory Group)

Table 6: Additional comments regarding registration timelines

	Additional Comments (combination of Regulatory and Export group responses)
1.	They vary, some take longer than others.
2.	mostly between 1 and 2 years
3.	It will be easier if the MCC registration could accelerate the process
4.	Some are less than 1-2 year. SA and Botswana timelines tend to distort the average timelines.
5.	Varies from <1 to >3 from country to country
6.	It depends per country - some quicker some slower
7.	Here again this time line is country dependent, some countries approve in 6 weeks, others 6 months and other 2 years
8.	Depends on the country. Namibia 1 year. Botswana can be more than 3 years
9.	Varies, depending on the country

The responses and comments indicate that the timelines are variable and therefore not consistent. Only about **50%** of medicines are registered in 2 years.

An efficient, predictable registration timeline will promote access to new medicines and encourage more companies to register medicines in Africa.

Table 7: Anecdotal remarks by survey respondents regarding country specific regulatory requirements

	Additional Comments (combination of Regulatory and Export group responses)
1	Labelling requirements; GMP inspections
2.	Currently have products registered in Namibia only. We have had no serious problems regarding registration to date.
3.	Certain countries do not have the expertise to deal with registration of biologics
4.	Requirements are extremely diverse from region to region.
5.	To some extent. We have come up with ways to address this, but the biggest area of concern is post registration relating to technical and safety variations.
6.	Different country requirements for labels definitely presents a huge problem.
7.	Specific requirements, particularly regarding packaging, are a challenge

5.5.1 Recognition of International Standards

The recognition of international standards is particularly important in countries and regions that have resource constraints. International standards contribute greatly to companies ability to comply with regulatory requirements and from the regulator's point of view, in ensures not only that high standards are maintained that are in line with international best practice, but also assists with functioning optimally in a resource constrained environment.

Below is a snapshot of companies experience in the 4 major economic regions in Africa as to whether international standards are recognized.

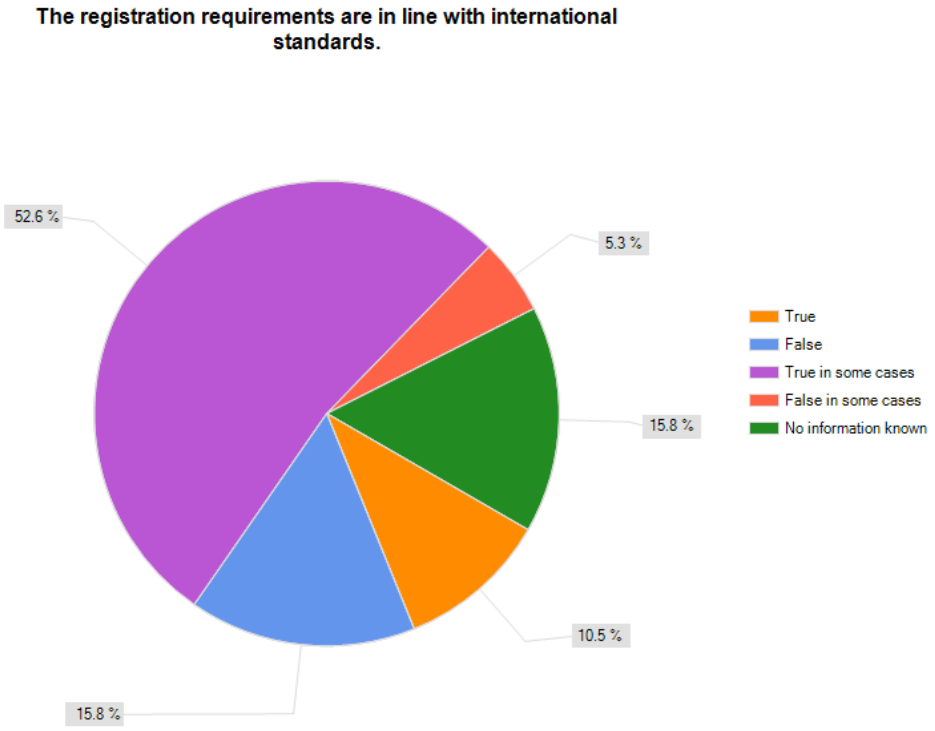


Figure 4: African registration requirements compared to international standards – overall view (Regulatory group)

Table 8: Registration requirements are in line with International Standards

Region*(no. of companies)	True (%)	False (%)	True in some cases (%)	False in some cases (%)
EAC (11)	9.1	18.2	54.5	9.1
ECCAS (8)	12.5	0	62.5	12.5
ECOWAS (8)	12.5	12.5	50	12.5
SADC (15)	13.3	13.3	60	6.7

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group)

Table 9: Lack of **recognition** of international standards

Region*(no. of companies)	Yes (%)	No (%)
EAC (10)	90	10
ECCAS (6)	85.7	14.3
ECOWAS (7)	85.7	14.3
SADC (15)	86.7	13.3

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group)

Although the results were mixed in terms of whether current African medicines registration requirement are in line with international standards, some respondents indicated that there is a level of alignment with international standards, which is very positive while some responded that there was a lack of recognition of international standards. As part of the harmonization process, the regulatory status of medicines by benchmark authorities should be recognized. It is also important that African countries maintain their sovereignty in making regulatory decisions. An ideal scenario would be a combination of recognizing international standards and the sovereignty of African countries without increasing the complexity of registering medicines in African countries.

5.5.2 GMP[2] Inspections

GMP inspections have been cited by most companies operating in African countries as a barrier to registration and supply of medicines. As per Table 10 below, the majority of companies are of the opinion that GMP inspections are a barrier to registration of medicines in Africa. Specific country trends were also assessed to gain a more detailed view of areas of specific concern.

Table 10: Views on whether GMP Inspection requirements are a barrier to registration of medicines

Region*(no. of companies)	Yes (%)	No (%)	No Opinion (%)
EAC (11)	77.8	9.1	22.2
ECCAS (7)	85.7	0	14.3
ECOWAS (6)	71.4	0	28.6
SADC (14)	57.1	7.1	35.7

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group)

[2] GMP = Good Manufacturing Practice

5.5.3 Country-specific trends

Results indicated that GMP inspections are particularly problematic is specific countries, as per Table 11.

Table 11*: Countries where companies experience problems with GMP inspections

SADC	ECOWAS	EAC	ECCAS
Tanzania	Ghana	Kenya	None
South Africa	Nigeria	Uganda	
Botswana	Togo		
Mozambique			
Zimbabwe			

*Combination response of Regulatory and Export groups

5.5.4 Recommendations for improvement

Table 12: Anecdotal recommendations for improvement of the GMP inspection process

	Recommendations (combination of Regulatory and Export group responses)
1.	I have not experienced these yet. I'm still new in the Africa registration side .I've since done registrations in Kenya and Botswana only.
2.	Delays the process, increases expenses for product registration. Regulators must share information with other regulators. In other countries there are no set rules as a result you do not know what to do.
3.	Have a one centralized GMP inspection that the HA can use it for approval of our submission, this will reduce a fee paid to each individual country. These countries are small markets and there is no guarantee that the company will make its return should they wish to register and pay the inspection fee e.g. Ghana they require USD 15,000.
4.	Use FDA, PIC approvals.
5.	Accept MCC as the regulatory authority for registration and inspection purpose.
6.	Acceptance of inspection status from "competent" authorities
7.	Collaboration between regulatory bodies - acceptance of other regulatory body audits.
8.	Costs are in many instances exorbitant and not always once off. In some instances the cost of GMP inspections do not warrant sale of the product in that country.
9.	Accepting results from GMP inspections by recognizes regulatory authorities.
10.	Need harmonised criteria for animal health products especially pesticide manufacture
11.	Recognition of inspection outcomes of PICs member countries for instance. Alternatively, harmonised inspection for the economic area
12.	Mutual recognition

5.5.5 GMP Inspection Fees

GMP inspections are used as a key source of income in some countries. Survey respondents were asked about the level of fees that need to be paid for GMP inspections in the 4 economic regions.

Table 13: GMP Inspection fees by region

Region*(no. of companies)	Too high (%)	Appropriate (%)	Too low (%)	Unknown (%)
EAC (10)	70	10	0	20
ECCAS (7)	71.4	14.3	0	14.3
ECOWAS (7)	57.1	14.3	0	28.6
SADC (15)	46.7	13.3	0	40

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group)

The majority of companies indicated that GMP inspection fees are too high. One respondent commented that the cost of follow-up inspections was too high in relation to the frequency of inspections required (3 to 4 years).

A key consideration for African Regulatory harmonization is the recognition of the international GMP status of manufacturing sites. The potential impact of increased number and frequency of GMP inspections include:

- Potential delays in approval
- Medicines supply as some sites shut down during a GMP inspection e.g. Sterile manufacture cannot continue during GMP inspections
- The cost of GMP inspections could be a deciding factor in whether companies persue registration in a country.

6 Commercial Perspective

The commercial perspective of the supply of medicines to Africa, although controversial is an important consideration, especially in light of the importance of economic growth promotion in these countries. Another important aspect to consider is the level and impact of infiltration of medicines or lack of availability into these markets that have or could potentially have a negative public health impact on the populations of these countries.

85.7% (6 companies) indicated that they have made a decision not to supply medicines into African markets. Specific countries mentioned included Ghana, Nigeria, Ethiopia, Tanzania, Kenya, Uganda, Mozambique and Zimbabwe.

The reasons for these decisions are as follows: (Export group response)

Table 14*: Reason for discontinuation of supply of medicines in specific African markets

Reasons for decision not to supply medicines in African countries	% response (no. of companies)
Commercial	71.4 (5)
Lengthy registration timelines	28.6 (2)
Registration costs	57.1 (4)
Retention Costs	42.9 (3)
Unregistered medicines already available	14.3 (1)
Risk of counterfeit medicines	14.3 (1)
Generic equivalents already available	14.3 (1)
GMP Inspection fees	42.9 (3)
GMP inspection requirements	28.6 (2)

*export group responses

When asked specifically about whether decisions to not supply medicines in specific markets related to regulatory issues, the results were as follows.

Table 15: Percentage of companies discontinuing supply of medicines in African markets related to regulatory reasons

Region*(no. of companies)	Yes (%)	No (%)
EAC (10)	50	50
ECCAS (6)	50	50
ECOWAS (7)	57.1	42.9
SADC (14)	28.6	57.1

*This is a subset of companies that indicated that they supply medicines in these regions (Export group and Regulatory groups)

When asked in which markets these decision have been made, the response included Ghana, Uganda and Sudan.

Other comments included:

'The cost of maintaining the product is higher than the returns.'

'Insistence on GMP inspections have resulted in us not pursuing registrations in some countries. Sales volumes do not justify high costs.'

'Sales do not cover registration renewal fees.'

Of further concern is that **7** companies indicated that they had cases of counterfeit medicines of their products.

6.1 Interrupted Supply

85.7% of respondents indicated that they had experienced instances where they were unable to supply medicines into African markets. The reasons cited for the interrupted supply were all related to regulatory requirements related to medicines registration. One respondent cited concerns of product diversion to Western countries as the reason.

There has been feedback of medicines being held at customs indefinitely due to regulatory requirements, e.g. country specific labeling such as the out pack of the medicine not having the registration details of the country printed on it.

The majority of companies have experienced instances when they have been unable to supply medicines to specific markets. As per table below, approximately 50% of companies have been affected with the exception of supply to the SADC region.

Table 16: Companies experiencing instances of interrupted supply of medicines to specific regions

Region*(no. of companies)	Yes (%)	No (%)	Not Applicable (%)
EAC (10)	50	40	10
ECCAS (6)	50	33.3	16.7
ECOWAS (7)	57.1	28.6	14.3
SADC (14)	35.7	50	14.3

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group)

The respondents were also asked to supply reasons for the interrupted supply to determine a link, if any, to regulatory requirements. The reasons cited included the following:

'Zambia: specific labeling requirements prohibited supply.' (Cited twice)

'Delays in approval of post registration amendments.'

'If stringent labeling requirements are enforced we might not be able to supply medicines.'

'Waiting for approval of new manufacturer.'

It is clear that there is a link between the levels of interrupted supply, which are quite high, and the regulatory requirements. The lack of alignment with international standards, impact of counterfeit medicines, GMP inspections, unpredictable registration and approval timelines, have impacted and will continue to impact product supply, unless changes are made to country-specific requirements as well as the recognition of international standards.

6.2 Public Health Impact of Current Regulatory Requirements

Survey respondents were asked about their views on the public health impact of the current requirements for registration of medicines in African markets. There were strong views expressed regarding the delayed access to medicines and the resultant impact on the health outcome of patients, i.e. hospitalisation due to uncontrolled disease or in some cases death as a result of lack of treatment availability. This in turn increases the burden on the rest of the healthcare system and therefore increases the overall cost of healthcare.

Another view was that having stringent regulatory requirements would contribute to keeping counterfeit medicines out of the market. Ethiopia was cited as an example of good management in this regard by requiring that medicines need to be on the EDL[3] before it can be registered.

Some anecdotal remarks:

'Patients unable to get good quality medicines. Overall cost cannot be measured on cost of drug alone. Other factors need t be considered depending on the type of drug, i.e. length of hospital stay, recovery time, etc.'

'Takes a very long time to launch, market and sell a new product in the African export markets – specialists and their patients do not have access to new drugs (impacts on their quality of life).'

'Lack access to best available drugs results in sub-optimal treatment and continues the cycle of poor disease treatment and control in Africa. Undue suffering and death.'

'Unfortunately our drug is a chronic medication used to treat chronic renal disease patients. This specialized market is not fully addressed due to the low numbers of physicians and nephrologists and so many patients go undetected and untreated and as a result experience a poor quality of life due to anaemia as a result of renal disease.'

'The public health impact is high. Access to safe, effective quality medicines is essential and any barriers to access means that the public may not receive the product timeously or may never receive a product essential to their well being.'

'Delay in access to medicines, in some instances, where there is no alternate treatment.'

6.3 African Medicines Registration Harmonisation Initiative

The views expressed by most respondents were very positive. 82% of respondents are positive about the AMRHI. A lot of focus and emphasis was placed on the need for implementation. It was felt that previous attempts at achieving harmonisation failed due to lack of political will and commitment to implementation.

Some comments:

[3] EDL = Essential Drugs List

'I fully support the concept. I believe the continent will benefit greatly from the process, not only making good quality medicines available but bringing in a lot of investment to all countries. If the concept is not put into action then it will remain merely a concept.'

'Fantastic if it can be implemented.'

'Very good if it can be effective.'

'The process must be fast tracked.'

'All stakeholders should be involved in this process.'

'Africa and the various economic regions within Africa have been speaking about harmonisation for quite some time now, but we cannot put our differences aside to make progress.'

'Must expedite this process so we can have harmonized regulation requirements even in key areas such as GMP inspections and labeling.'

7 Recommendations

PIASA supports the AMRHI project. In order to achieve the objectives of this project, we believe that broad consultation and input from key industry stakeholders is essential. Key insights can be gained from input from pharmaceutical companies operating in these markets from a practical perspective. Key principles that need to be considered by Regulatory Authorities include:

- The risk of over-regulation and its resultant impact on medicines access and public health
- Adopting systems of benchmark agencies in a resource constrained environment
- Approval status of products by benchmark agencies to optimise regulatory approval processes

We support the objectives of the AMRHI project, which are ambitious and will be achieved over time. There is, however, a pressing need to address some of the regulatory burdens in the short term, which will not only alleviate the current issues experienced by companies, but will also contribute positively to the achievement of the objectives of the AMRHI. In this regard, we propose that interim agreements be established between regulators and the pharmaceutical industry to alleviate the negative impact on medicines access in African markets. In particular, we would like to propose the following:

1. Recognition of well-established international standards i.e. ICH guidelines [4]e.g. the Common Technical Dossier (CTD), [5]the use of ATC classification for products
2. Optimise regulatory capacity and resources by having training of Africa's evaluators

[4] ICH Guidelines – International Conference on Harmonisation; globally recognised standard

[5] CTD = Common Technical Dossier, international standard format used for the submission of dossiers for the registration of medicines.

3. Implement an African system for pharmacovigilance on medicines to track product defects and safety surveillance of medicines
4. Harmonisation of product labeling standards and requirements to ensure market access of products
5. Recognition of the international regulatory approval by benchmark countries i.e. US, EU, Canada, Australia
6. Harmonisation of Product Renewals [6]processes
7. Post marketing changes / variations aligned with ICH guidelines
8. Recognition of the international GMP status of manufacturing site i.e. acceptance of PIC/S [7]GMP reports

8 Conclusion

The AMRHI initiative is welcomed by PIASA. There is, however, an immediate need for interim processes to be established with great urgency to reduce the impact of interrupted supply of medicines in African markets as well as reduced investment by pharmaceutical companies who cannot comply with country specific requirements. PIASA recommends that the project team place great emphasis on this with urgency. Interim agreements such as recognition of internationally accepted standards will also go a long way in establishing and embedding the principles of harmonisation.

Furthermore, current regulatory requirements should be carefully scrutinized to determine whether they are value-adding or non-value adding to the process. In this way, the current registration processes can be streamlined, thereby shortening the overall registration timeline for medicines.

The benefits of harmonized medicines registration processes are far reaching and can be summarized as follows.

[6] Product renewals = process required to ensure that the registration of a particular medicine is still current

[7] PIC/S = The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

Figure 5: Benefits of Harmonisation

All the key stakeholders in the medicines value chain will gain from a successful implementation of the AMRHI with a positive impact on the health status of the populations of African countries.

PIASA would welcome the opportunity to provide further input into the AMRHI project and work in partnership with members of the project team to ensure the successful implementation of harmonized medicines registration processes.