Making the case: how regulatory harmonisation can save lives in Africa

More than 23,000 lives could be saved by accelerating access to two health products by two years

PATH

455 Massachusetts Avenue NW
Suite 1000
Washington, DC 20001 USA

www.path.org

Suggested citation: *Making The Case: How Regulatory Harmonisation Can Save Lives In Africa*. Washington, DC: PATH; 2018.

Published December 2018

Photo: PATH/Eric Becker

New ideas for lifesaving health products are generated everyday, but they are only impactful if they reach the people who need them most. Regulatory harmonisation has shown promise in several regions in Africa to accelerate the advancement of medical products through the regulatory process, thereby helping them achieve scale and save lives, faster.

Introduction

Significant disparities in health outcomes around the world are driven by unequal access to essential health products.

Scientific advances have led to the creation of new vaccines, medicines, diagnostics, and devices that have saved millions of lives. Yet new products may not be readily accessible to those in need due to a variety of factors, including systemic challenges caused by weak regulatory oversight, particularly in low- and middle-income countries (LMICs).

A recent study found that the lag in regulatory approval of new health products in sub-Saharan Africa is typically four to seven years after first regulatory submission in high-income countries.[1] These delays can mean the difference of life or death for patients waiting for access to these proven treatments.

Many national regulatory authorities in LMICs are under-resourced and overburdened because of competing priorities. As a result, these countries are unable to robustly and comprehensively regulate the safety and efficacy of essential health products, which delays the review process and hinders timely access to quality-assured health products. Compounding this situation is the fact that regulatory processes differ from country to country, resulting in delays for researchers and manufacturers, who must navigate multiple regulatory systems to register the same health product across multiple countries.

To address these challenges, a number of efforts are underway in sub-Saharan Africa to harmonise regulatory activities and accelerate access to safe and effective products across the region. The African Union Model Law on Medical Products Regulation (AU Model Law; see Box 1) has provided a framework for member states to increase collaboration across countries, strengthen regulatory capacities of partner states, and accelerate the registration of high-quality, safe health products. This is achieved through pooling resources and expertise, sharing information, providing technical assistance, and increasing collaboration to ensure the efficient evaluation of products.

Despite the political support and progress made to date, many regulatory harmonisation efforts across Africa remain in early stages and are not yet equipped to address regulatory challenges holistically. Major barriers to bringing harmonisation to scale include an overreliance on a small number of funders, limited and varied technical capacities, limited bandwidth of current initiatives, and a lack of commitment to resources and action. For example, though governments have shown strong interest, much of the funding for harmonisation efforts to date has come from

Box 1: AU Model Law

In January 2016, the African Union Heads of State adopted the Model Law on Medical Products Regulation, which is meant to guide national governments and regional economic communities (RECs) to harmonise regulatory systems and increase collaboration across countries. A country can adapt the AU Model Law to ensure alignment with its constitutional principles and legal system—and amend or repeal inconsistent national laws. Once adopted and implemented by RECs and countries, the goal of the AU Model Law is to resolve discrepancies in current regulatory legislation and improve the efficiency and effectiveness of regulatory systems.

donors such as the World Bank, World Health Organization, United Kingdom Department for International Development, and the Bill & Melinda Gates Foundation.[2] These donors have been instrumental in initiating harmonisation efforts, but a lack of long-term, more varied funding is a major obstacle to sustainability. Further, though harmonisation efforts have demonstrated success, such as the joint assessment of products or clinical trials, these initiatives could be strengthened and equipped to regulate the full spectrum of health products or support regulation across all regulatory phases, including clinical trials, pharmacovigilance, and post-marketing quality assurance. Adoption of the AU Model Law was a critical first step, but implementation will require long-term commitments, sustained funding, and political action at multiple levels of government and across regions. To note, though the term harmonisation is used throughout the analysis, we recognise that some countries are moving towards the use of the term convergence, to imply alignment, rather than uniformity of regulatory requirements. For the sake of this analysis, harmonisation is being used in the broadest sense to include sharing information, providing technical assistance, and increasing collaboration to ensure the efficient evaluation of products.

The following analysis explores the potential impact of regulatory harmonisation on accelerating access to health products. More specifically, PATH estimated the number of lives that could be saved by accelerating the timeline for registration and scale-up of two emerging medicines—aimed at preventing postpartum haemorrhage (PPH) in women during childbirth and treating pneumonia in children under the age of five.

Photo: PATH / Andrew Berends

A healthcare worker in Kenya visits with a postpartum mother. Postpartum hemorrhage is a leading cause of maternal death in Africa.

Through the use of modelling, PATH determined that accelerating access to two products due to regulatory harmonisation could contribute to more than **23,000 lives saved** in eastern and southern Africa. In order to fully realise the potential health impact of harmonisation across Africa, sustained commitments—political, financial, and technical—are required from policymakers and donors alike.

Policy Recommendations

Fund regulatory harmonisation across Africa to enable scale-up.

Ensure all regulatory phases and functions are harmonised across products.

Domesticate the AU Model Law in all AU member states.

Modelling Background

To strengthen the case for regulatory harmonisation, PATH conducted an analysis to estimate its potential health impact in terms of lives saved. To illustrate this impact, we selected two regional economic communities (RECs) on which to focus the analysis: the East African Community (EAC) and Zazibona.

These regions were selected because of progress made relative to other harmonisation initiatives, but their efforts could still be accelerated. For example, the EAC was the first REC to begin implementation of the African Medicines Regulatory Harmonisation (AMRH) initiative, and notable achievements include the development of technical documents and joint dossier assessments, and the registration of new products.[3] Similarly, the Zazibona initiative, which is a collaboration between national medicines regulatory authorities in Botswana, Namibia, South Africa, Zambia, and Zimbabwe, has already reviewed more than 156 health products and registered more than 50 for use.[4]

Prior to the start of regulatory harmonisation efforts in the EAC, it was estimated that the average standard registration time for medicines was 24 months.[5] A study from Janssen Pharmaceuticals, Inc., examined the impact of joint assessments amongst EAC countries and found that regional joint reviews lessened the review time for medicines amongst participating countries by 40% to 60%, from one to two years down to seven months.[6]

Building on this evidence, this analysis is designed to quantify the potential health impact of approving and launching medicines in RECs faster. It assumes that medicines would reach the market one to two years faster if they were approved and launched in each REC through a harmonised regulatory process.*

The two medicines that are modelled in this exercise are a heat-stable formulation of carbetocin to prevent PPH in mothers, and a dispersible tablet formulation of amoxicillin to treat pneumonia in children under the age of five (see Box 2). The analysis of these two medicines is not intended to provide a complete estimate of the value of regulatory harmonisation, but rather to provide two examples of the potential benefits of regulatory harmonisation in different populations: mothers and children under the age of five.

Box 2: Medicines Modelled

For this analysis, the following criteria were used to select products: medicines had to 1) be appropriate for use in LMICs, 2) address health areas that affect either mothers, newborns, or children under the age of five, and 3) be in late stage clinical development (phase III or later) or relatively early in their global commercial launch. The products selected were:

Heat-stable carbetocin

Postpartum haemorrhage, or severe bleeding after childbirth, is the leading cause of maternal death globally.[7] Oxytocin is the recommended intervention for effectively preventing and treating PPH, though this drug is not available to many women, especially in remote areas. It currently comes in liquid form and needs to be injected. Oxytocin must be stored at controlled room temperature (25°C or lower) or in refrigerated storage (2°C to 8°C) in order to ensure quality.[8] Access to electricity and refrigeration is inconsistent in LMICs, creating barriers for many to accessing this lifesaving drug. In order to combat these issues and improve access, heat-stable carbetocin, which has been shown to be as effective as oxytocin at preventing PPH, has been developed.[9]

Amoxicillin dispersible tablets

Pneumonia is the leading infectious cause of death in children under five globally. An estimated 920,000 children died from pneumonia in 2015, accounting for 16% of child deaths.[10] However, pneumonia-related mortality is preventable with appropriate case management, including oral antibiotics (such as amoxicillin). Dispersible tablets are the World Health Organization's recommended treatment for childhood pneumonia and have several advantages over other formulations of amoxicillin. The tablets are less expensive than amoxicillin oral suspension; have logistical and supply chain advantages in terms of volume and weight; are designed to accommodate patients with difficulty swallowing; do not require refrigeration; and facilitate and simplify integrated community case management with greater dosage accuracy compared to oral suspension, which must be manually measured and mixed.

* The Lives Saved Tool is only capable of modelling increased access to products in full year increments.

Methodology

The Lives Saved Tool (LiST),[11] developed by the Johns Hopkins Bloomberg School of Public Health, was used to estimate the potential health impact of accelerated access to essential medicines in regions where regulatory activities were harmonised as compared to regulatory reviews conducted country by country. Specifically, the model was used to quantify the potential number of lives saved due to earlier access to heat-stable carbetocin and amoxicillin dispersible tablets.

The model was applied to all EAC countries (Burundi, Kenya, Rwanda, Tanzania, and Uganda) and all Zazibona countries (Botswana, Namibia, South Africa, Zambia, and Zimbabwe) participating in the AMRH initiative at the time the modelling was conducted. Countries were modelled separately, and data were aggregated for each region. Different launch timing assumptions were made based on scenarios in which the medicines were approved, introduced, and scaled in each region through a harmonised or non-harmonised regulatory process. In addition to a baseline scenario that assumed the approval and launch of products with no regulatory harmonisation, two different scenarios were modelled in which it was assumed that regulatory harmonisation would lead to either a one- or two-year faster time to market.

A peak, or maximum, coverage rate was estimated to occur five years after the product launch (see Appendix 1). This exercise applied a linear scale-up in coverage, and assumed a 20% increase in coverage for each product in its appropriate setting over its comparable product (see Appendix 2). To understand the impact of regulatory harmonisation, the difference in lives saved by year was estimated between the baseline non-harmonised scenario and the two harmonised scenarios over the forecast period.

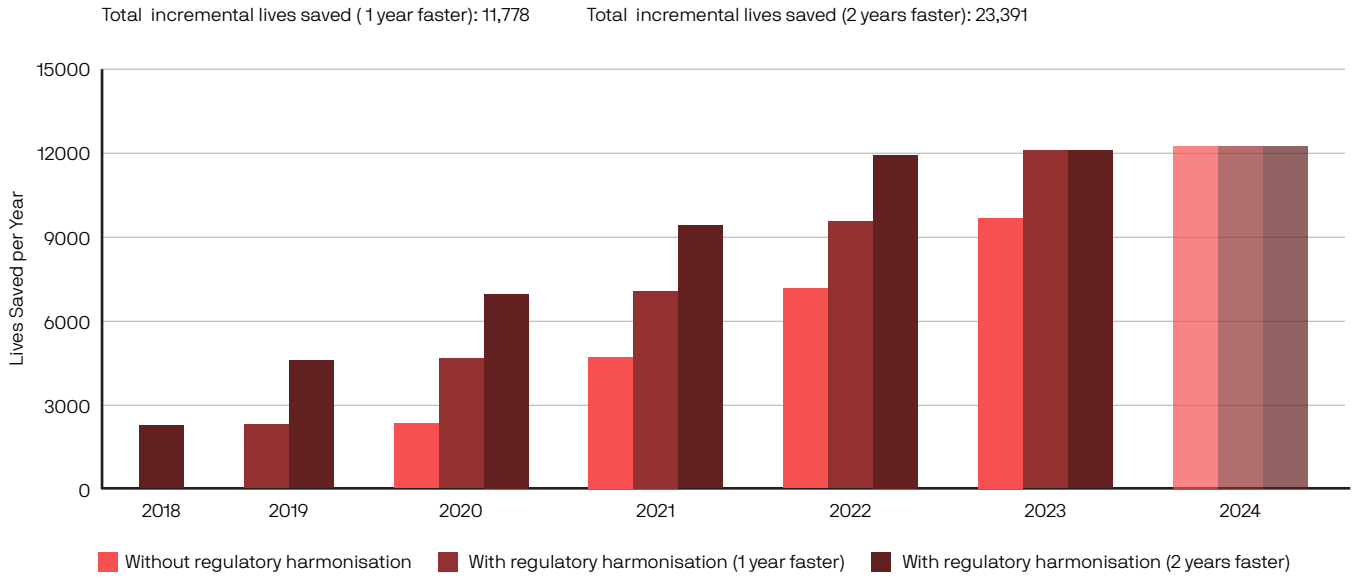
Results

The modelling results demonstrate that accelerating approval and launch timing by one or two years due to regulatory harmonisation can have substantial impact on saving lives (See Figure 1 for summary and Appendix 3 for detailed results).

On average, there are approximately 45,000 and 19,000 deaths in children under five due to pneumonia each year in the EAC and Zazibona countries, respectively.[11] The results of this modelling conclude that launching dispersible tablets two years earlier in all countries could save almost 16,000 more lives in EAC countries and almost 7,000 in Zazibona countries over the non-harmonised scenario, given the coverage estimates and timeline. Even when the launch is only accelerated by one year, approximately 8,000 and 3,000 more lives could be saved over the non-harmonised scenario in the EAC and Zazibona countries, respectively.

Absolute lives saved due to scaling up heat-stable carbetocin are more modest than amoxicillin in all scenarios because there are far fewer maternal deaths than child deaths in these countries. On average, there are approximately 4,000 maternal deaths in the EAC and 800 maternal deaths in Zazibona countries each year due to PPH.[11] However, accelerating the launch timing by two years due to regulatory harmonisation for heat-stable carbetocin can still save more than 800 lives in the EAC countries and 200 lives in Zazibona countries over the non-harmonised scenario.

FIGURE 1. **Total annual lives saved from launching amoxicillin dispersible tablets and carbetocin in the EAC and Zazibona from 2018-2023**



Key Limitations

It is important to acknowledge that there are several limitations when considering the results of this modelling exercise. For both medicines, it is recognised that registration is only one necessary component in launching a product and that registration alone does not guarantee these medicines will become available.

This analysis assumes that heat-stable carbetocin will reach regulatory milestones and begin its global launch in 2018. However, it is possible that this launch may be delayed or not occur. Amoxicillin dispersible tablets were already available in some markets when this analysis was undertaken, but given the need to scale more broadly, it was selected for this analysis.

It should also be noted that these two medicines alone do not represent the total impact of regulatory harmonisation; they are designed to be used as case studies to highlight what is possible for select emerging medicines. Lastly, regulatory harmonisation efforts have improved since the modelling exercise occurred, thus the baseline model scenario may underestimate the recent progress.

Conclusions

Even though regulatory harmonisation has been endorsed at the highest political levels within the AU and efforts to harmonise regulatory policies across RECs are already having positive impacts, progress continues to be slow across Africa. This analysis adds to the evidence for increased investment in regulatory harmonisation and convergence by demonstrating the potential impact—measured in lives saved—that it can have on accelerating access to essential health products, specifically in eastern and southern Africa.

To accelerate the scale-up of regulatory harmonisation and improve access to essential health products for underserved populations, political commitment must be paired with a commitment to providing resources. Sustainable funding must be mobilised from donor and domestic funders; harmonisation efforts must be expanded to cover different types of products and across regulation phases; and the AU Model Law must be enshrined into law by each member state. Without tangible commitments, current efforts will not overcome regulatory challenges sustainably.

Fund regulatory harmonisation across Africa to enable scale-up

The lack of sustained funding for regulatory strengthening, overreliance on a small number of external donors for core funding, and limited domestic investment because of competing priorities limit pervasive change needed to make large-scale impact. The lack of a long-term vision for more varied funding, particularly amongst African countries, is a major roadblock to sustainability. This funding deficit is further compounded by limited technical expertise and bandwidth.

Successful harmonisation will require a long-term vision and sustained funding from a more diverse group of funders. Funding from international donors should help leverage greater domestic investment, which will be required to bring harmonisation to scale across Africa.

Ensure all regulatory phases and functions are harmonised across products

Promising progress through initiatives like AMRH in the EAC and Zazibona have demonstrated the impact that harmonisation can have in accelerating access to lifesaving medicines. However, these initiatives—and others across Africa—could be strengthened. Though this analysis looks specifically at medicines, there is currently a gap in the regulation of diagnostics, critically important to ensuring timely and accurate treatment, as well as medical devices. In addition to the need to cover the full spectrum of health products (drugs, devices, vaccines, and diagnostics), harmonisation must also expand across all regulatory phases.

Accelerating access to lifesaving products will require a sustained commitment to building out the scope of ongoing initiatives, including a commitment to sufficiently staffing and building technical expertise to support a range of products across all regulatory phases—including clinical trials, pharmacovigilance, and post-marketing quality assurance.

Domesticate the AU Model Law on in all AU member states

The AU Model Law is the framework upon which countries can model their participation in regional regulatory activities. However, to have any impact, the legislation must be adopted and enforced by each country. Though advancements have been made across the continent, many gaps and challenges in realising the full implementation of the AU Model Law remain. Several countries, including South Africa, have passed legislation expanding the mandate of their national regulatory bodies and aligning their regulatory systems with harmonisation efforts. But South Africa is in the minority, and the resourcing of these new regulatory authorities has been slow.

To overcome these barriers and accelerate access to safe and effective products, the public and private sectors in high-, middle-, and low-income countries must work together to close the funding gap, strengthen regulatory capacity and infrastructure, and prioritise strong regulatory systems as a driver for economic and social growth.

Appendices

Appendix 1. Key model timing assumptions.

Scenarios	Assumed launch year	Assumed year of peak coverage
No regulatory harmonisation (baseline scenario)	2020	2024
Regulatory harmonisation with one year earlier time-to-launch	2019	2023
Regulatory harmonisation with two years earlier time-to-launch	2018	2022

Appendix 2. Baseline and peak coverage rates of interventions in the Lives Saved Tool

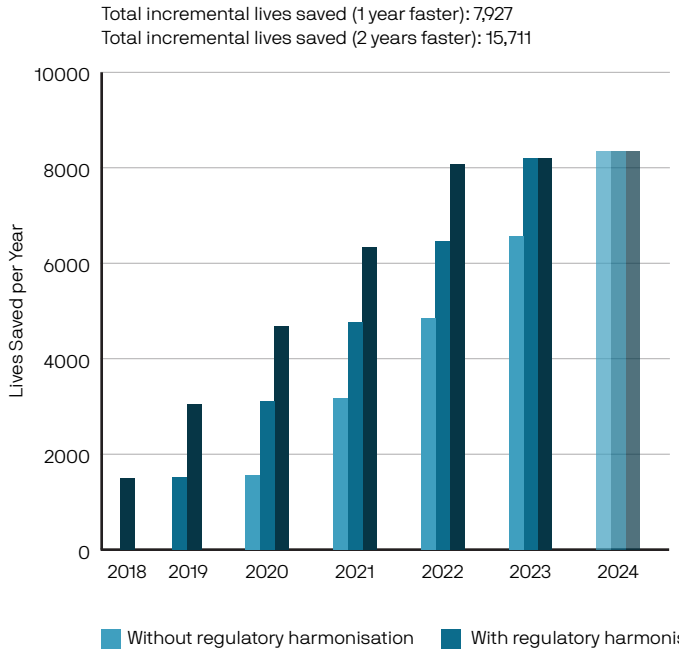
		Injectable uterotonics		Oral antibiotics for pneumonia	
	Country	Baseline coverage of oxytocin (2017)[1]	Assumed peak coverage (5 years post-commercial launch of heat-stable carbetocin)	Baseline coverage of oral antibiotics for pneumonia (2017)[2]	Assumed peak coverage (5 years post-commercial launch of amoxicillin dispersible tablets)
EAC	Burundi	44.6%	53.5%	54.7%	65.6%
	Kenya	46.1%	55.3%	65.7%	78.9%
	Rwanda	68.0%	81.6%	53.9%	64.7%
	Tanzania	46.9%	56.3%	55.4%	66.5%
	Uganda	43.0%	51.6%	78.7%	94.4%
ZAZIBONA	Botswana	70.4%	84.5%	14.0%	16.8%
	Namibia	65.5%	78.6%	67.7%	81.2%
	South Africa	66.5%	79.8%	73.2%	87.9%
	Zambia	48.2%	57.8%	69.7%	83.6%
	Zimbabwe	57.7%	69.2%	50.9%	61.1%

(1) Baseline coverage rates in LiST for heat-stable carbetocin are for active management of the third stage of labour, which includes oxytocin. Oxytocin is a similar injectable uterotonic to carbetocin and is currently available in some settings to prevent and treat postpartum haemorrhage.
(2) Baseline coverage rates in LiST for amoxicillin dispersible tablets are for oral antibiotics for pneumonia (e.g., syrups). These represent other oral formulations of amoxicillin that are currently available in some settings for treatment of childhood pneumonia.

Appendix 3. Detailed results, by product and region

FIGURE 2. Modelling results demonstrating the potential impact of regulatory harmonisation for amoxicillin dispersible tablets

Annual lives saved from launching amoxicillin dispersible tablets in the EAC from 2018-2023



Annual lives saved from launching amoxicillin dispersible tablets in Zazibona from 2018-2023

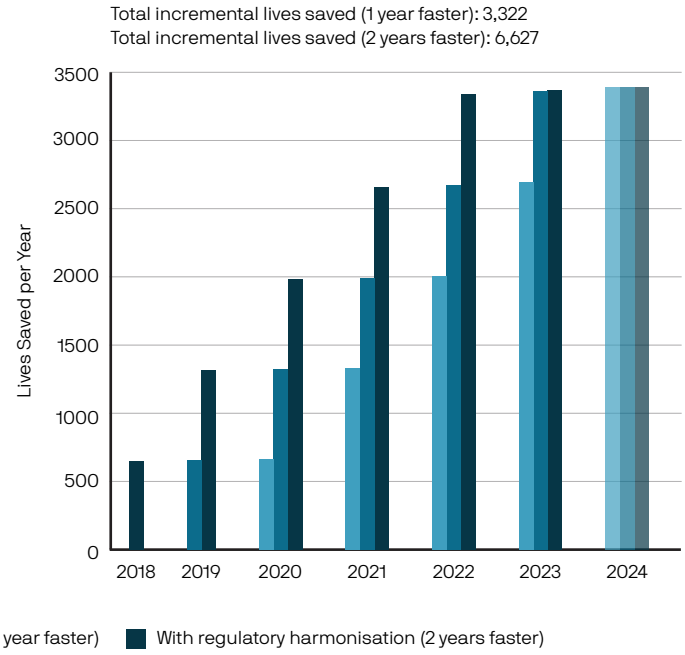
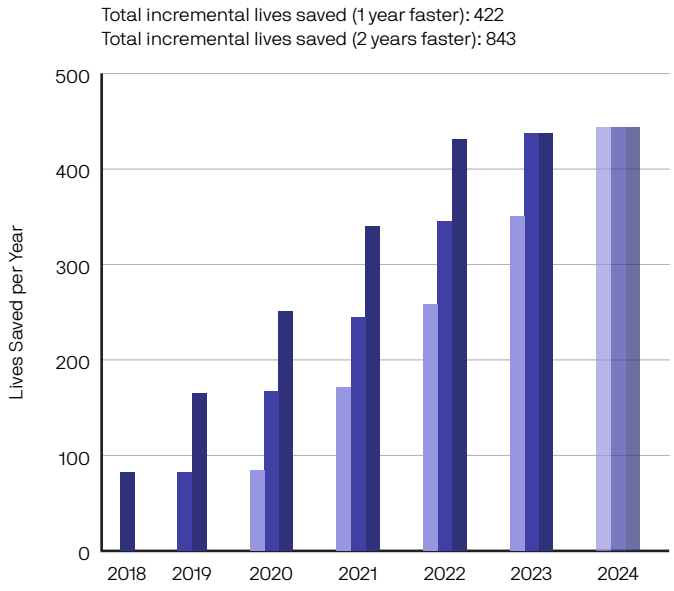
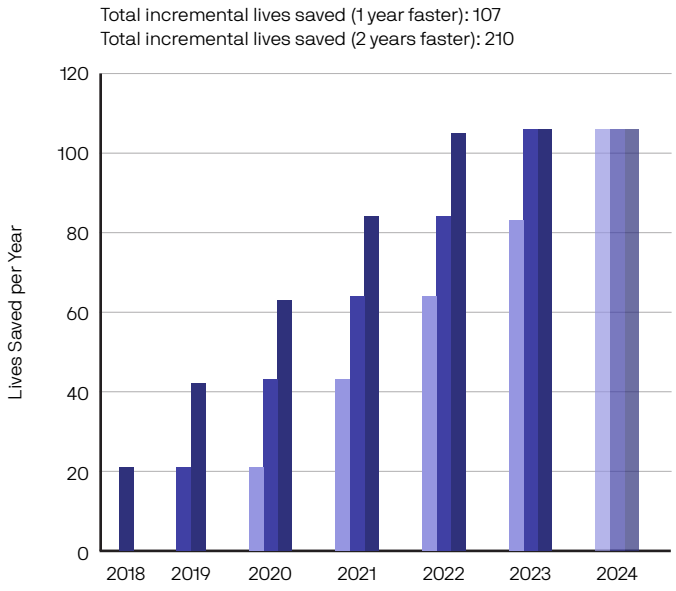


FIGURE 3. Modelling results demonstrating the potential impact of regulatory harmonisation for heat-stable carbetocin

Annual lives saved from launching heat-stable carbetocin in the EAC from 2018-2023



Annual lives saved from launching heat-stable carbetocin in Zazibona from 2018-2023



Endnotes

1. Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding access to vaccines and medicines in low- and middle-income countries: a case for change and a framework for optimized product market authorization. *PLOS ONE*. 2016;11(11):e0166515. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166515.
2. PATH. *Medicines Regulation in the East African Community: Landscape Summary Report*. Seattle, WA: PATH; 2016. http://www.path.org/publications/files/APP_eac_reg_summary.pdf.
3. The African Medicines Regulatory Harmonization (AMRH) Initiative: Accomplishments, challenges and path forward. Presented at: 17th International Conference of Drug Regulatory Authorities, 27 November–2 December 2016; Cape Town, South Africa. http://www.icdra.co.za/images/Presentions_Sunday/Sun_27_Nov_09h00_Ndomondo_Sigonda.pdf.
4. World Health Organization website. Essential medicines and health products: Improving the quality of medical products for universal access page. http://www.who.int/medicines/regulation/fact-figures-qual-med/en/. Accessed 6 November 2018.
5. Kamwanja LA, Saka J, Awotedu A, Fute I, Chamdimba C, Ndomondo-Sigonda M. *Situation Analysis Study on Medicines Registration Harmonisation in Africa: Final Report for the East African Community (EAC)*. Pretoria, South Africa: New Partnership for Africa's Development; 2010. http://www.nepad.org/resource/situation-analysis-study-medicines-registration-harmonisation-africa-final-report-east.
6. Johnson & Johnson. Janssen Pharmaceuticals Inc pilot study. https://pink.pharmaintelligence.informa.com/PS119980/Janssen-Pilot-Speeds-Up-African-Approvals-As-Harmonization-Project-Expands.
7. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health*. 2014;2(6):e323-e3-33. doi: 10.1016/S2214-109X(14)70227-X.
8. Reproductive Health Supplies Coalition. Oxytocin brief. Caucus on New and Underused Reproductive Health Products; 2012. https://path.azureedge.net/media/documents/RHSC_oxytocin_br.pdf.
9. Shakur-Still H, Roberts I. Finding better ways to prevent postpartum hemorrhage. *New England Journal of Medicine.* 2018; 379(8) 790 792. https://www.nejm.org/doi/full/10.1056/NEJMoa1805489#article_citing_articles.
10. World Health Organization website. Pneumonia: Key facts page. 7 November 2016. http://www.who.int/en/news-room/fact-sheets/detail/pneumonia. Accessed 6 November 2018.
11. The Lives Saved Tool website. Version 5.61. http://livessavedtool.org. Accessed November 2017.

455 Massachusetts Avenue NW
Suite 1000
Washington, DC 20001 USA

info@path.org
www.path.org