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COMMISSION STAFF WORKING DOCUMENT

REFIT EVALUATION

of the

**Council Regulation (EC) 953/2003 to avoid trade diversion into the European Union of
certain key medicines**

{SWD(2016) 125 final}

Contents

Section 1:	Introduction	Error! Bookmark not defined.
	<i>Purpose of the evaluation</i>	Error! Bookmark not defined.
	<i>Scope of the evaluation</i>	Error! Bookmark not defined.
Section 2:	Background to the initiative	Error! Bookmark not defined.
	<i>Description of the initiative, its objectives and the problems it was intended to solve</i>	Error! Bookmark not defined.
	Bookmark not defined.	
	<i>Rationale</i>	Error! Bookmark not defined.
	<i>Description of the Regulation</i>	Error! Bookmark not defined.
	<i>Baseline</i>	Error! Bookmark not defined.
Section 3:	Evaluation questions.....	Error! Bookmark not defined.
Section 4:	Method.....	Error! Bookmark not defined.
	<i>Process</i>	Error! Bookmark not defined.
	<i>Data collection by CRA</i>	Error! Bookmark not defined.
Section 5:	Implementation.....	Error! Bookmark not defined.
	<i>Application of the Regulation</i>	Error! Bookmark not defined.
	<i>Conclusion</i>	Error! Bookmark not defined.
Section 6:	Answers to the evaluation questions	Error! Bookmark not defined.
	<i>How effective has the EU intervention been?</i>	Error! Bookmark not defined.
	<i>Conclusion</i>	Error! Bookmark not defined.
	<i>How efficient has the EU intervention been?</i>	Error! Bookmark not defined.
	<i>How coherent is the EU intervention internally and with other action?</i>	Error! Bookmark not defined.
	defined.	
	<i>How relevant is the EU intervention?</i>	Error! Bookmark not defined.
	<i>What is the added value of the EU intervention in support of tiered pricing?</i> ..	Error! Bookmark not defined.
	defined.	
Section 7:	Overall conclusions	Error! Bookmark not defined.
Annexes.....		Error! Bookmark not defined.
Annex 1:	Procedural information.....	Error! Bookmark not defined.
Annex 2:	Stakeholder consultation	Error! Bookmark not defined.
Annex 3:	Methods and analytical models used in preparing the evaluation	Error! Bookmark not defined.
	defined.	

Section 1: Introduction

Purpose of the evaluation

Council Regulation (EC) No 953/2003 was included in the Commission's regulatory fitness and performance (REFIT) programme in 2013,¹ as it had been used only to a limited extent, thereby raising questions as to its relevance and effectiveness. The Commission had periodically reported to the Council on the application of the Regulation, but had not conducted a full review. It was therefore appropriate to carry out an evaluation to understand why its use had been so limited.

The purpose of the evaluation is to gain a better understanding of the Regulation's impact and assess whether it remains fit for purpose and minimises associated costs and burdens. The findings will be used to guide further action in pursuit of the Regulation's objectives, including decisions on possible amendment or repeal.

Scope of the evaluation

The evaluation covers the Regulation's functioning and impact from its adoption until 2015. An external contractor, CRA, was commissioned to gather data to evaluate the Regulation.²

Section 2: Background to the initiative

Description of the initiative, its objectives and the problems it was intended to solve

The Regulation was intended to contribute to increasing the supply of affordable HIV/AIDS, TB and malaria medicines to the poorest developing countries.

It was part of a 2001 Commission action programme on HIV/AIDS, malaria and TB³ aimed at achieving the sixth UN Millennium Development Goal (MDG): to halt and reverse the spread of HIV/AIDS, malaria and other major diseases by 2015. The programme included other action such as increased support for R&D programmes on health, development programmes for the supply of essential medicines in developing countries, stronger pharmaceutical policies and capacity-building, and enhancing the impact of health and population intervention targeting the major communicable diseases and poverty reduction. By the end of the 1990s, approximately six million people a year were dying from HIV/AIDS, TB and malaria, the vast majority in developing countries. In Africa, HIV/AIDS was not only the primary cause of death, but also the biggest challenge to development.

The price of medicines was one source of concern, as many were too expensive for developing countries. In 1996, an effective HIV/AIDS therapy came out, but it cost €10 000 per person per year, which developing countries could not afford. If access to medicines in the developing world was to improve, prices needed to be brought down.

¹ COM(2013) 685.

² The study and all other documents relating to the evaluation are available at: <http://ec.europa.eu/trade/policy/accessing-markets/intellectual-property/access-to-medicines/>

³ *Programme for action: accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction*, Commission Communication to the Council and the European Parliament (COM(2001) 96 final).

In 2000, the Accelerating Access Initiative, a partnership between UNAIDS, the WHO and pharmaceutical companies, started to do this. By December 2001, the cost of drugs provided under the Initiative had dropped significantly, in some cases to 10–20 % of their price in industrialised countries. The cost of a first-line regimen fell from USD 10 000 to around USD 350. About 27 000 people had gained access to therapy, a nearly 10-fold increase in the number of patients treated.

Lower prices alone were not enough, as even the price of treatment at cost exceeded the annual income of many in the LDCs.

In 2002, the Global Fund was set up to finance HIV/AIDS, malaria and TB medicines in developing countries, with the EU as a significant contributor. In 2003, the United States President's Emergency Plan for AIDS Relief (PEPFAR) set aside USD 15 billion for HIV/AIDS prevention, care and treatment programmes.

In order to charge lower prices for developing countries, producers needed assurance that discounted products would not be diverted to high-income markets and sold at high prices. The risk of this grew with the significant increase in the volumes of discounted products. Further increases were to be expected, as the WHO estimated that the number of people in need of therapy would grow from 230 000 at the end of 2001 to 3 million by 2005.

Two cases show the difficulty of addressing product diversion before the Regulation was in place. In 2002, several consignments of GSK's HIV/AIDS medicines intended for African aid programmes ended up on the European market. The products had been sold to *L'Afrique pour l'Afrique* under the Accelerated Access Initiative at 15 % of the western market price (the EU market value was €15 million). In the first case, the Belgian health authorities notified their Dutch counterparts on 30 July 2002 of a suspicious shipment entering Antwerp from Africa, addressed to a Dutch wholesaler and parallel importer, Asklepios. At the authorities' request, Belgian customs did not release the shipment. In August, GSK had the shipments seized. In the second case, GSK's products never reached Africa, but were diverted to UK hospitals.

In both cases, GSK went to court but was held to blame for the diversion, because the products destined for Africa were not differentiated. They bore the standard French packaging with EU registration numbers, indicating approval for sale in Europe. There were no stickers, warnings or colour changes to indicate that the goods were for sale only in Africa. Both courts concluded that third parties could have regarded them as being on the European market legitimately and that it would have been appropriate to differentiate products by packaging or otherwise. The Dutch court awarded GSK only 40 % of its damages. In the UK, GSK lost on 15 of the 16 charges. The message for manufacturers was that goods destined for non-EEA countries should be clearly marked. Companies therefore needed to use differentiated packaging to protect against diversion.

Rationale

The Regulation was adopted to implement the Commission's 2001 action programme, under which the Community was *inter alia* to establish a tiered pricing system for key pharmaceuticals for these diseases for the poorest developing countries. That approach was supported by the Council, in a resolution on 14 May 2001, and the European Parliament, in a resolution on 15 March 2001. The Regulation sent a signal of support for tiered pricing.

Action at EU level was needed, as customs regulations did not authorise customs to seize parallel-traded medicines re-imported into the EU. The Regulation empowered customs to suspend the release of, or detain, registered products.

The EU-level action programme was necessary to foster sustainable development so as to eradicate poverty in developing countries (an objective of Community development policy).

The rationale for intervention was to offer protection against the risk of re-import into the EU in response to producers' potential objections to significantly increasing supplies of medicines in the poorest developing countries at heavily discounted prices.

The Regulation was to provide a safety net for manufacturers. As noted above, courts had considered that manufacturers of tiered-price products must differentiate their appearance so as to prevent product diversion. By obviating the need for other anti-diversion mechanisms (different packaging, product and batch traceability programmes, etc.) and for communicating these to customs authorities, the Regulation helped to reduce costs.

The Regulation also aimed to improve transparency as regards the prices at which HIV, TB and malaria medicines were sold to developing countries, by requiring companies to report on the volume and prices of registered products they supplied and the Commission to issue regular public reports on products registered, and prices and volumes sold.

Rationale			
Objectives	Tools	Output	Impact
➤ prevent tiered-price products from being imported into the EU; ➤ encourage producers to make products available to the poorest countries at heavily reduced prices in significantly increased volumes; ➤ improved transparency of prices at which HIV, TB and malaria medicines are sold to developing countries; ➤ signal EU commitment to tiered pricing	Customs control via logo	No trade diversion; easier identification by customs	Increased volumes at heavily reduced prices
	Price control via formulae	Reduced prices	Increased access
	Reporting by companies on volume and prices	Regular public reports from Commission	Verifiable data to increase trust in tiered pricing

Description of the Regulation

Manufacturers or exporters of pharmaceutical products can submit applications to register HIV/AIDS, malaria and TB medicines supplied at low prices to any of 76 countries (including all LDCs).

To benefit from the Regulation, products must be priced no higher than 25 % of the weighted average ex-factory OECD price or involve a mark-up of no more than 15 % on direct production costs. Application must give sufficient detail for the price to be verified.

An expert committee with representatives of Member States' medicines regulatory authorities assesses the applications.

Re-import into the EU is prohibited. A permanent logo is to be affixed to any packaging or registered product sold at tiered prices to the countries of destination, so customs can easily identify and stop re-imports.

Companies must submit annual sales reports for each tiered-price product to the Commission, which must periodically report to the Council on the volumes exported under tiered prices.

Baseline

The extent of product diversion at the time of the Regulation is hard to quantify, as diversion is illegal and only detected cases are recorded. The study identified the two cases of diversion described above before the Regulation came into force.

At the time of the introduction of the Regulation, around 400 000 people in need in low- and middle-income countries were estimated to have access to HIV/AIDS medicines.⁴ There were almost 300 million cases of malaria worldwide each year and over a million people died. Nearly 90 % of these deaths occurred in sub-Saharan Africa, where young children were the most affected. Malaria was directly responsible for one in five childhood deaths in Africa.⁵ There were 8 million new cases per year of TB and nearly 2 million deaths, over 95% of which were in low- and middle-income countries. In 2000, the World Health Assembly endorsed the establishment of a Global Partnership to Stop TB. Unlike for HIV/AIDS, there were few patented innovative medicines for malaria and TB.

Section 3: Evaluation questions

In line with the Commission's evaluation guidelines and the evaluation mandate, CRA assessed the Regulation on four criteria:

- **effectiveness:** to what extent did it achieve its goals of preventing tiered-price products from being imported into the Union and encouraging the pharmaceutical industry to make pharmaceutical products available to the poorest developing countries at heavily discounted prices?
- **efficiency:** were the costs justified, given the achievements? (This includes in particular an assessment of administrative burden for businesses, especially SMEs);
- **coherence:** to what extent is it coherent internally, with other EU policies, with Treaty objectives and with the activities of other actors?
- **relevance:** to what extent do the (original) objectives (still) correspond to EU needs?

The guidelines mention five standard criteria: the four mentioned here, plus 'EU added value'. This is not covered in this study, as the Regulation relates to matters falling within the scope of the common commercial policy (Article 207 TFEU); this is recognised as an exclusive competence under Article 3 TFEU, so only action by the EU is possible.

An EU regulation is required to achieve the objective of ensuring that customs prevent HIV/AIDS, TB and malaria medicines sold to the poorest developing countries at discounted prices from being re-imported into the EU. Action at EU level was needed, as the existing

⁴ World Health Organisation (2013), Global Health Observatory (GHO) data:
http://www.who.int/gho/hiv/epidemic_response/ART_text/en/

⁵ 1999 *World Health Report*.

rules did not authorise customs to seize re-imports of parallel-traded medicines into the EU. The Regulation empowered customs to detain, or suspend the release of, registered products.

Section 4: Method

Process⁶

The evaluation started in January 2014, when a steering group was set up. On 6 June 2014, the steering group validated the evaluation mandate and terms of reference for an external contractor commissioned to gather data to evaluate the Regulation. Following a call for tender, a contract was signed with CRA on 5 December 2014.

Under a roadmap published in January 2015, the provisional results of CRA's study were to be made available online on 1 July and a workshop on these was to be held in Brussels on 15 July. Given the specialised subject area, it was decided that a targeted consultation should be conducted as part of the study rather than an internet-based public consultation.

On 17 June, a month before the workshop, an announcement was sent to DG TRADE's civil society dialogue mailing list and published on the DG TRADE website.

CRA interviewed all stakeholders that had been active in the field, including pharmaceutical industry and international organisations, civil society organisations dealing with access to medicines, and Member State authorities, in particular those dealing with pharmaceutical products, health and trade. It also interviewed companies, key non-governmental organisations (NGOs), academics and experts in the field.

As planned, the provisional results of the study were made available on DG TRADE's website on 1 July and discussed at a workshop on 15 July in Brussels with 40 stakeholders from pharmaceutical industry and international organisations, academics and representatives of civil society organisations dealing with access to medicines, and Member State authorities. Stakeholders had until 22 July to provide written comments; three did so.

CRA delivered its final report, taking into account the written comments and those received at the workshop, as planned by 5 August.

Data collection by CRA

Effectiveness: CRA carried out a literature review and a press/media search on trade diversion, and reviewed the Commission's reports on the implementation of the Regulation. It interviewed DG TAXUD experts, customs officials in Belgium and the Netherlands (where the two cases of product diversion had occurred before the Regulation was adopted), national regulatory agencies and a number of pharmaceutical companies and NGOs.

To analyse the impact on the price and volume of medicines supplied to the 76 countries covered by the Regulation, CRA collected data from the WHO global price reporting mechanism (GPRM),⁷ this database records purchases of HIV/AIDS, TB and national programmes to supply malaria medicines in low- and middle-income countries. This data was

⁶ The annexes contain detailed information on the process and the methodologies used.

⁷ <http://www.who.int/hiv/amds/gprm/en/>

cross-checked against other sources such as the Global Fund's price and quality reporting (PQR) system.

To glean stakeholders' views on the history and impact of the Regulation, CRA conducted interviews with eight industry participants and four NGOs involved in access to medicine.

Efficiency: CRA interviewed Commission officials, customs authorities and the industry, including GSK, to determine costs and benefits.

Coherence: CRA reviewed the coherence of the Regulation on the basis of literature and interviews with Commission experts, NGOs and the European Federation of Pharmaceutical Industries and Associations.

Relevance: CRA used results from the analysis of the Regulation's impact on trade diversion, and on the price and volume of medicines. In addition, it conducted a literature review on the access to medicines debate, which covered academic literature on tiered pricing and material from pharmaceutical companies that operate tiered-pricing mechanisms and organisations involved in the debate on tiered pricing.

To complement the desk research, CRA carried out interviews with eight academics, three international organisations, eight pharmaceutical companies, the European Federation of Pharmaceutical Industries and Associations and four NGOs involved in access to medicine.

The provisional results were presented and validated at the workshop. Participants from industry, academia and civil society organisations commented separately on the parts of the study addressing the four evaluation points.

Limitations – robustness of findings

The Regulation was adopted at a time when impact assessments were not obligatory and there is no official document outlining the baseline at the time, nor data on the market situation or the need for a regulation to address product diversion. Neither, therefore, was there an assessment as to the potential impact of the Regulation. As a result, assessing its effectiveness in preventing product diversion required a historical reconstruction of the situation at the time of adoption to see if the initiative had brought about any change. This was done on the basis of literature research, combined with interviews with several people involved in drafting the legislation. Customs experts were also consulted.

To assess the Regulation's effectiveness in encouraging the pharmaceutical industry to make products available at heavily discounted prices, data on the number of products supplied under the Regulation and on prices was readily available in the Commission's monitoring reports. Also, data was available from verified sources such as the GPRM on total amounts of medicines provided outside the Regulation and, to a large extent, their prices.

The reasons for the low uptake of the scheme were assessed on the basis of literature research, combined with interviews of academic experts, NGOs and companies producing HIV, TB or malaria products that qualified for registration under the Regulation.

Reliable data from the Commission's impact assessment of the falsified medicines legislation was used to assess packaging costs. Data provided by GSK and other companies was used to assess the costs of other anti-diversion measures. Although subjective, these were the best

possible estimates of the costs of these measures, as this is private confidential business information.

Coherence and relevance were assessed on the basis of literature research, combined with interviews of academic experts, WHO, the Global Fund, the UN-supported Medicines Patent Pool, NGOs and companies producing HIV, TB or malaria products that qualified for registration under the Regulation.

The overall robustness of the findings was further strengthened by a validation workshop. All interviewees were provided with the preliminary findings two weeks before the workshop and given the chance to comment. At the workshop, each part of the study was presented and discussed separately by participants from NGOs, academia and industry. All participants confirmed that the study and its conclusions were properly argued and well founded.

Section 5: Implementation

One company, GSK, used the mechanism created by the Regulation. The expert committee approved its application in 2004 and the products in question were included in the list of tiered-price products in Annex I to the Regulation on 28 October 2004. Annex I was amended on 11 October 2005, as GSK had differentiated two tiered-price products with red tablets from the white tablets sold on the EU market.

In line with the monitoring arrangements in Article 11 of the Regulation, GSK submitted annual reports of volumes and prices for each tiered-price product to the Commission.

The Commission periodically reported to the Council on the volumes exported. The reports indicated the importing countries and what diseases the medicines were for, and gave an assessment of the application of the price formulae in the Regulation. Eight reports were published. The most recent (16 December 2014) covers the years 2012 and 2013.

The Commission established a website with information on all registered products.⁸ The website also lists all Commission reports and provides information for manufacturers who wish to register a new product.

Application of the Regulation

EU customs authorities have reported no cases of product diversion under the Regulation.

After initial high sales, the volume of GSK's HIV medicines sold under the Regulation declined significantly. The total sales volume in 2013 represented just 3 % of that in 2005. This drop is explained by two factors:

- GSK granted 14 licences for these medicines to generic manufacturers and customers buy from them; and
- customers are purchasing other medicines that replaced GSK's as WHO 'preferred therapy'.

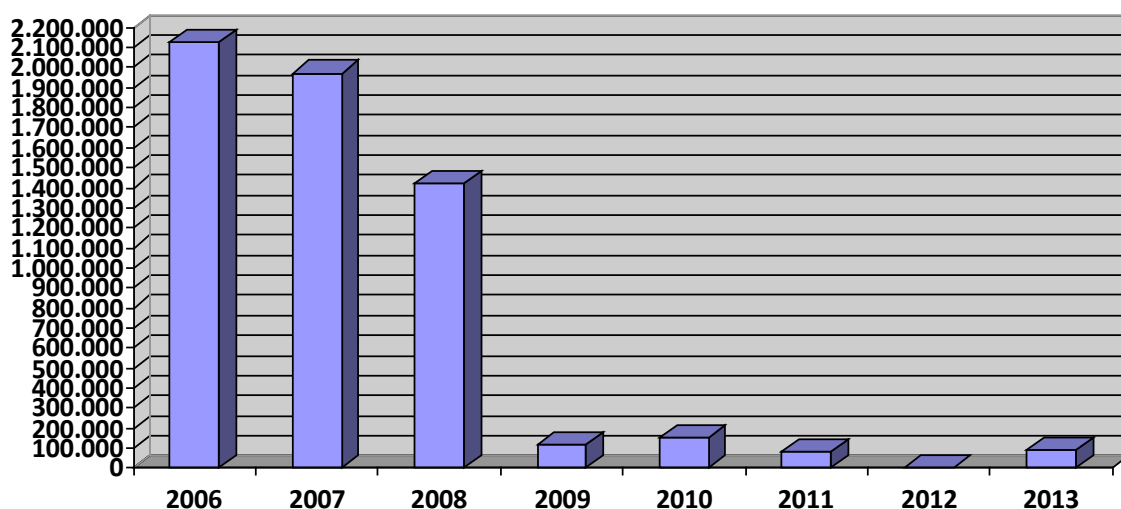
⁸ <http://ec.europa.eu/trade/policy/accessing-markets/intellectual-property/access-to-medicines/>

GSK's medicines represented an important contribution to HIV treatment. In 2011, ViiV Healthcare⁹ and licensees supplied an estimated 717 million packs of Epivir and Combivir to African countries. This is the equivalent of a year's supply for over a million people.

In some cases, the reported volumes vary greatly from year to year, because generic companies sometimes ran out of stock and could not supply. Governments or NGOs then asked ViiV to supply medicines at very short notice.

The figure below gives the sales volumes of products registered under the Regulation until 2013, the last year for which public data was available (see report of 16 December 2014).

Total sales volumes of packs of registered tiered-price medicines



The overall context of access to medicines

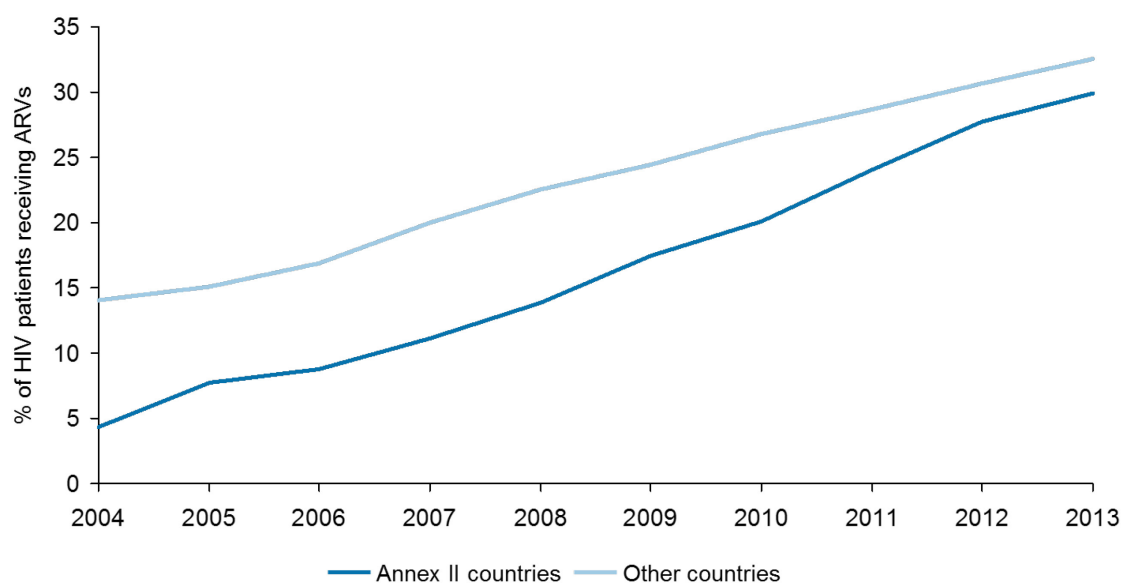
In order to understand the context of the Regulation, we need to look at developments as regards access to medicines. Access to HIV/AIDS, malaria, and TB medicines has improved substantially since the 2000s.

⁹ GSK set up a joint venture with Pfizer in November 2009, with both companies transferring their HIV assets to the new company, ViiV Healthcare.

HIV/AIDS

The number of people with access to HIV/AIDS medicines grew rapidly following the introduction of the Regulation, from 400 000 in 2003 to 11.7 million by the end of 2013. The sixth UN MDG target of reaching 15 million people with antiretroviral (ARV) drugs by the end of 2015 was achieved nine months ahead of schedule. The percentage of HIV patients treated increased in countries listed in Annex II to the Regulation and other countries. The number of AIDS-related deaths also fell between 2005 and 2013.

Percentage of HIV patients treated with ARVs

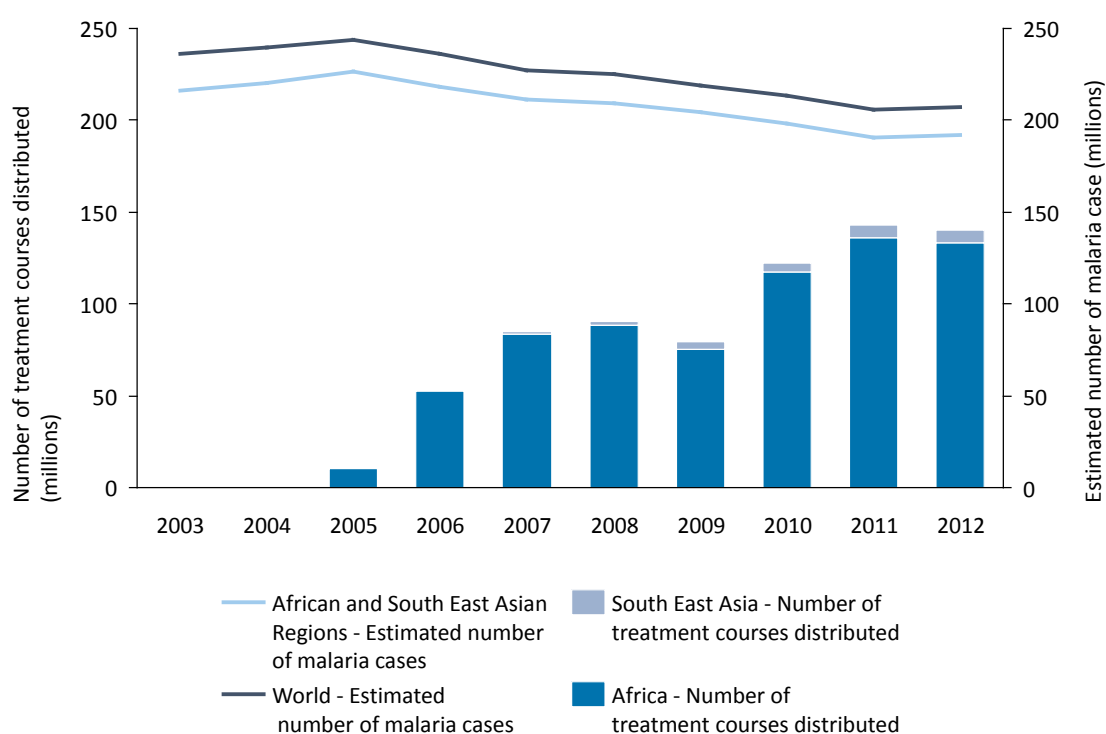


Source: UNAIDS database. Number of people receiving ARVs divided by the number of people with HIV.

Malaria

There has also been a major improvement in access to malaria drugs. The MDG 6 malaria target has been met. Of 106 countries with ongoing transmission of malaria in 2000, 64 are meeting the target of reversing the incidence of malaria and 55 countries are on track to reduce their malaria burden by 75 %, in line with the World Health Assembly's 2015 target. Malaria mortality rates decreased by 47 % between 2000 and 2013 globally, and by 54 % in the WHO African Region. Between 2000 and 2013, an expansion of malaria interventions helped reduce incidence by 30 % globally, and by 34 % in Africa.¹⁰

Estimated number of malaria cases 2003-2012 and number of treatment courses distributed



Source: CRA analysis using WHO Global Health Observatory Data 2014

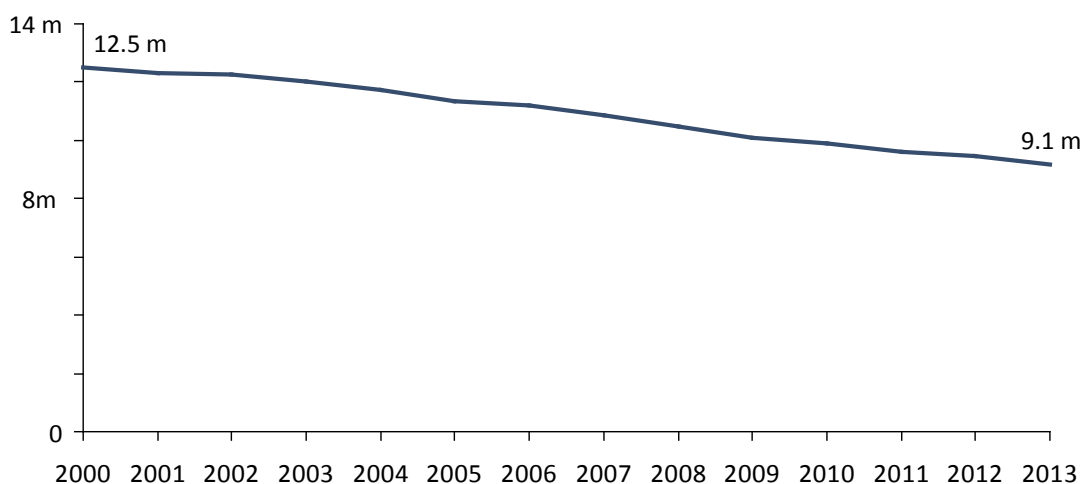
However, malaria transmission still occurs in 99 countries around the world, largely in sub-Saharan Africa. About 15 million pregnant women still have no access to preventive treatment for malaria and the disease is still responsible for over 430 000 child deaths in Africa every year. Emerging drug and insecticide resistance continues to pose a major threat, and there is a need for access to new products.

¹⁰ WHO, *World Malaria Report 2014*; http://www.who.int/malaria/publications/world_malaria_report_2014/en/

Tuberculosis

The MDG of halting and reversing TB has been achieved by all WHO regions and most of the high-burden countries. According to the WHO's *Global Tuberculosis Report 2014*, prevalence fell from 15 million people in 2001 to 11 million in 2013, i.e. by 27 %. Mortality dropped from 16 million to 1.1 million in the same period.¹¹

Number of prevalent TB cases in countries covered by the Regulation



Source: CRA analysis using WHO Global Health Observatory data for 2014.

According to the Global Fund, 67 % of people with TB were diagnosed in 2013, as compared with 43 % in 2003. Of those who receive treatment, approximately 85 % are successfully treated, an 18 % increase from 2003.¹²

Conclusion

Although the volume of HIV medicines that GSK sold under the Regulation declined significantly, more were supplied overall via licences to generic manufacturers. GSK's medicines represented an important contribution to HIV treatment. In 2011, medicines sold under the Regulation and by licensees represented a year's supply for over a million people.

Since the 2000s, access to medicines for all three diseases has improved substantially, but challenges remain, particularly for HIV/AIDS, where 65 % of patients remain without access, but also for TB and malaria.

¹¹ WHO (2014), *Global Tuberculosis Report*; <http://www.who.int/tb/country/data/download/en/>

¹² Global Fund (2013), *The Global Fund to Fight AIDs, Tuberculosis and Malaria – fourth replenishment (2014-2016): update on results and impact*; <http://www.theglobalfund.org/en/replenishment/fourth/reports/>

Section 6: Answers to the evaluation questions

How effective has the EU intervention been?

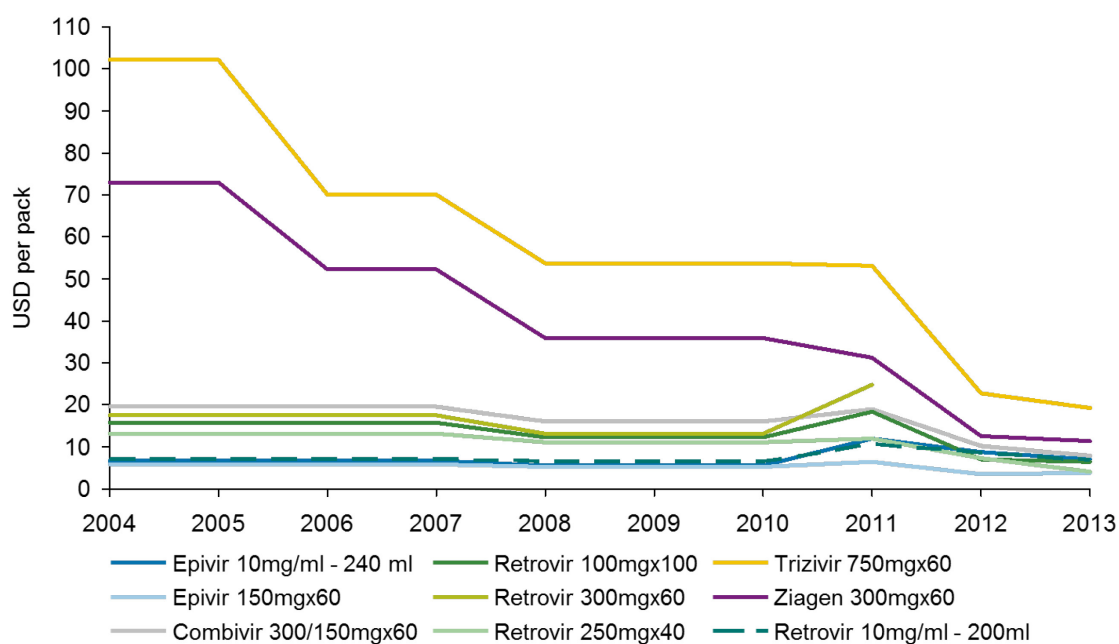
CRA assessed the impact of the Regulation on volumes and prices to see if it had achieved the objective of *‘encourag[ing] pharmaceutical producers to make pharmaceutical products available at heavily reduced prices in significantly increased volumes by ensuring ... that these products remain on those markets’*.

Sales volumes of GSK products registered under the Regulation were initially high, reflecting the importance of GSK’s HIV/AIDS medicines at the time. However, volumes fell dramatically as of 2009, as GSK adopted a strategy of voluntary licensing, whereby generic manufacturers make the products and customers buy from them. Also, treatments from other companies grew in importance.

CRA analysed the period 2004-2008, when sales volumes of the GSK products were still substantial, and found that the Regulation had a positive impact. On average, countries covered by the Regulation purchased increased volumes of registered molecules (+79 %).

CRA found that prices in those countries generally declined after 2004, but many factors were changing and there is no statistically significant difference between the tiered price of Regulation products and that of others. GSK’s prices did not fall after it registered products, as it was already making its products available at 15 % of the western market price (under the Accelerated Access Initiative), which is in line with the price requirements of the Regulation. The list prices of the same products in OECD countries were stable between 2005 and 2011.

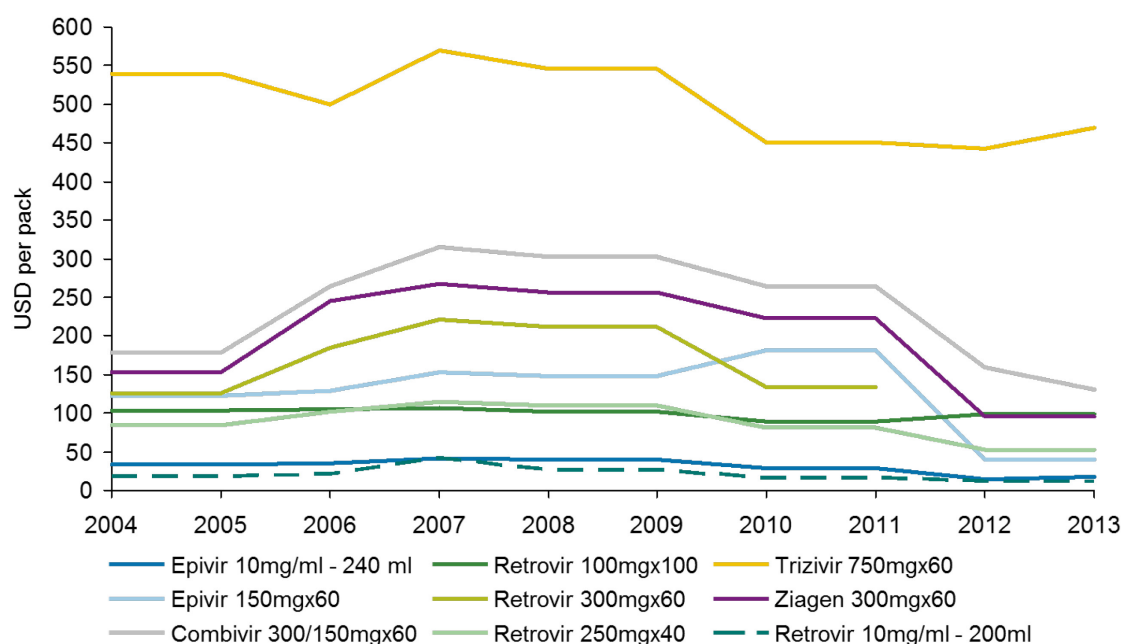
List prices per pack for products in countries covered by the Regulation, 2004-



2013

Source: Annexes to report on Regulation (EC) No 953/2003, 2003-2013

OECD lowest list prices per pack for Regulation products, 2004-2013



Source: Annexes to report on Regulation (EC) No 953/2003, 2003-2013

CRA found no evidence of customs having seized Regulation products. However, it is not possible to attribute this solely to the Regulation, as GSK took other measures to prevent product diversion. CRA found no evidence of other cases of trade diversion outside the Regulation and academic studies confirmed this.¹³

The threat of product diversion to the EU has not materialised to the extent feared at the time the Regulation was drafted, largely because:

- pharmaceutical companies found other ways to address the risk of diversion;
- the EU put more legal safeguards in place for medicine supply;
- PEPFAR and global institutions such as the Global Fund controlled supply chains better; and
- new national programmes significantly reduced the risk of diversion.

In interviews with CRA, some companies said that one factor influencing their decision not to register was that they felt that the Commission should not be involved in price-capping. As these companies' access prices were already below the maximum set by the Regulation, they would not have had to reduce them, but they objected to the principle of price-capping.

Although GSK was the only company to register products, the Regulation appears to have encouraged pharmaceutical producers to reduce prices by signalling EU support for tiered-pricing programmes. Many companies had access programmes for their HIV/AIDS medicines that included tiered pricing. For example, in May 2000, five companies¹⁴ signed up to the Accelerating Access Initiative to supply cheaper tiered-price products. The 2014 *Access*

¹³ M. Kyle, *Product diversion in pharmaceuticals*, report to DfID and IGFAM, 24 February 2015, p. 2.

¹⁴ Boehringer Ingelheim, Bristol-Myers Squibb, GSK, Merck and Hoffmann-La Roche, later joined by Abbott and Gilead.

to *Medicines Index* found that 15 of the 20 top pharmaceutical companies had advanced tiered-pricing ('equitable pricing') strategies in place.

Many stakeholders interviewed by CRA highlighted the benefit of the Regulation in signalling the Commission's approval of and commitment to tiered pricing. CRA concluded that the Regulation may have improved the dialogue between stakeholders on better access.

Conclusion

- CRA found no evidence that registered products were re-imported into the EU, but it is not possible to attribute this solely to the Regulation, as GSK took other anti-diversion measures.
- Use of the Regulation appears to have been limited, probably because the risk of product diversion did not appear to be significant.
- Some companies said that the price-capping under the Regulation influenced their decision not to register even though their products had prices below the ceiling.
- CRA found that the Regulation had not reduced prices, but had had a positive impact on the volumes of GSK products supplied between 2004 and 2008.
- Many industry stakeholders felt that the Regulation gave a useful signal of support for tiered pricing and contributed to a more constructive dialogue that ultimately helped improve access.

How efficient has the EU intervention been?

CRA found that the Commission had incurred only administrative costs in running the scheme. These pertain to the working time for introducing the Regulation, for the work of the expert committee and for drawing up annual reports. Overall, CRA estimated the costs at around 40 person/weeks. There were no costs for customs, as no additional action was required on top of their routine control activities.

GSK incurred costs in registering products with the Commission and adding a logo on the packs. CRA estimated these at around €200 000 for the whole period. There are also one-off costs of getting medicines regulatory authorities to amend/extend marketing authorisations due to changes in the packaging. As the fee for such amendments in several countries is estimated at over €100 000, CRA estimates the overall costs associated with the logo at several hundred thousand euros.

Other companies choosing to use the Regulation would face similar administrative and marketing authorisation costs.

As use of the scheme is voluntary, companies who do not use it were under no legal obligation to implement any measures and faced no additional administrative burden.

A logo can disappear in the event of repackaging, which is allowed under EU parallel-trade rules, so GSK used other, more costly tools. It differentiated two registered products in 2005, by producing red tablets instead of the white tablets sold in the EU,¹⁵ and also reformulated some products. These changes required regulatory approval in Europe and other countries

¹⁵ See *Annual Report (2004/2005) on the application of Council Regulation (EC) No 953/2003*, Commission staff working document (SEC(2006) 1256), p. 4.

where the products were sold, which in turn required evidence of comparable efficacy and safety. The approval procedure generated the biggest costs, which GSK estimates at several million euros.

The benefits of the Regulation include an offsetting of costs, as it reduced GSK's need to use other, more costly anti-diversion processes for some products in some areas. CRA concluded that it can be assumed that the administrative costs are offset by the benefits. Furthermore, the Regulation improved transparency on the prices at which HIV, TB and malaria medicines were sold to developing countries. Lastly, it sent a signal of support for tiered pricing. The benefits would be similar for other companies if they chose to use the Regulation.

Given that GSK continues to register its products under the Regulation and intends to register additional products, its administrative costs appear to be offset by the benefits.

Conclusion

- The reduction of the risk of product diversion was limited, but so were the costs. The Commission incurred administrative costs of around 40 person/weeks. GSK incurred costs of around €200 000 for the whole period in registering products and adding a logo on the pack.
- The costs of adding a logo and registering new package designs are relatively little (estimated at several hundred thousand euros) compared with the much higher costs of other anti-diversion strategies that required regulatory approval (several million euros). Therefore, the costs of using the Regulation do not appear disproportionate.
- Other companies choosing to use the Regulation would face similar administrative and marketing authorisation costs. Companies who do not use the scheme are under no legal obligation to take measures and face no additional administrative burden.
- The benefits of the Regulation include an offsetting of costs, as it reduced GSK's need to use other, more costly anti-diversion processes for some products in some areas. Furthermore, the Regulation improved transparency on the prices at which HIV, TB and malaria medicines were sold to developing countries. Lastly, the Regulation sent a signal encouraging the use of tiered pricing. These benefits would be similar for other companies choosing to use it.
- The costs of the EU intervention therefore appear proportionate to the benefits.

How coherent is the EU intervention internally and with other action?

To test the coherence of the Regulation with other initiatives, CRA examined Commission policies and initiatives that have links to key aspects of it, in particular:

- *EU legislation on medicines and trademarks*

EU medicines legislation ensures control over the entire distribution chain, from manufacture or import into the Union through to supply to the public. Since 2013, tougher rules¹⁶ have ensured protection against falsified medicines, giving customs and regulatory agencies greater means of monitoring the flow of medicines. These mechanisms will strengthen customs control, albeit with different legal bases for

¹⁶ Primarily, Directive 2001/83/EC, as amended by Directive 2011/62/EU.

intervention. This is coherent with the Regulation, as it can help in identifying infringing products.

In some cases, trademark laws provide tools for addressing infringements associated with parallel trade from outside the EU. The April 2015 trademark package reform will also reinforce customs control.¹⁷ This is coherent with the Regulation.

- *Trade policy measures on customs and international customs cooperation*

The Regulation is coherent with EU customs policies, in particular given the aim of improving the vigilance of EU customs, and measures focusing on customs enforcement, such as the EU customs action plan to combat intellectual property infringements¹⁸ and EU customs cooperation agreements.

The Regulation's aim of encouraging tiered pricing is consistent with the Commission's trade policy, which aims to help LDCs and other countries most in need to enjoy the benefits of trade for inclusive growth and sustainable development.¹⁹

- *International obligations and cooperation in the field of health and development*

One objective of the Commission's strategy on the EU's role in global health²⁰ is to keep essential medicines accessible and affordable, in line with the WTO Doha Declaration. The strategy committed the EU to the World Health Assembly's 2008 global strategy and plan of action, which aims *inter alia* 'to encourage pharmaceutical companies and other health-related industries to consider policies, including differential pricing policies'. CRA therefore found that the Regulation is coherent with the EU's global health policy.

CRA found that the Regulation is coherent with, and in fact highly complementary to, the EU's objectives and contributions to achieving the MDGs (in particular MDG 6) and its support for global financing initiatives such as the Global Fund.

CRA found that the Regulation is coherent with the recommendations of the Platform on Access to Medicines in Developing Countries on supporting approaches that facilitate the affordability of medicines through public/private partnerships.

CRA noted that the EU's 2013 *Report on policy coherence for development* also found that the Regulation is coherent with other action to promote access to medicines.²¹

Conclusion

- The Regulation is coherent with other EU policies and actions, in particular EU legislation on medicines and trademarks, and trade policy measures on customs and international customs cooperation, and highly complementary to the EU's international obligations and cooperation in the field of health and development.

¹⁷ http://ec.europa.eu/growth/industry/intellectual-property/trade-mark-protection/index_en.htm

¹⁸ *EU customs action plan to combat IPR infringements for the years 2013 to 2017* (2013/C 80/01).

¹⁹ *Trade, growth and development: tailoring trade and investment policy for those countries most in need*, Commission Communication to the European Parliament, the Council and the European Economic and Social Committee (COM(2012) 22 final).

²⁰ *The EU's role in global health*, Commission Communication (COM(2010) 128 final); http://ec.europa.eu/health/eu_world/global_health/index_en.htm

²¹ SWD(2013) 456 final.

How relevant is the EU intervention?

To assess the extent to which the original objectives of the Regulation still correspond to the EU's needs, CRA looked at:

- *To what extent is access to medicines still a significant challenge?*

Access to medicines for all three diseases has improved, but there are still patients without access. Of patients with HIV/AIDS, 65 % still have no access to ARVs. Many cases of TB are still undetected, over 80 % of cases are still being treated without diagnostic testing and access to new products needs to be improved. Malaria transmission still occurs and about 15 million pregnant women still have no access to preventive treatment for malaria. Malaria is still responsible for over 430 000 child deaths in Africa every year. Emerging drug and insecticide resistance continues to pose a major threat and access to new products is needed.

- *What contribution can tiered pricing make?*

CRA looked at the contribution tiered pricing can make in general to access to medicines by analysing academic literature and carrying out interviews. The academic view is that tiered pricing has a role to play, but its use varies considerably, depending for example on whether the same product is available on developing and EU markets.

NGOs expressed mixed views. The Bill & Melinda Gates Foundation supports tiered pricing but notes its limitations. Health Action International, Médecins Sans Frontières and Oxfam agree that it can allow for lower prices, but find generic competition preferable.

The pharmaceutical industry considers that tiered pricing leads to good results. It allows for prices that better reflect local levels of affordability, thus allowing industry to generate returns for innovation and giving society improved access.

Alternative types of access programme include voluntary licensing. Founded in 2010, the Medicines Patent Pool negotiates voluntary licences for generic manufacturers to use. It has accumulated agreements for 13 WHO 'preferred therapy' products now received by six million patients in 117 countries.²²

CRA noted that all types of programme have limitations and generally complement each other. Stakeholders recognised that tiered pricing still had some value, but there is now a range of other mechanisms, such as voluntary licensing and aggregated supply via the Global Fund, that make it less relevant.

- *Is there a role for policy intervention at EU level in support of tiered pricing?*

Several stakeholders expressed support for tiered pricing and a role for the EU. The industry stakeholders and the European Federation of Pharmaceutical Industries and Associations noted that policy should support voluntary differential pricing by companies. Academics expressed the view that tiered pricing has a role to play and the EU should show support for it.

²² *Working today for the treatments of tomorrow*, Medicines Patent Pool 2014 Annual Report.

The Access to Medicines Foundation encourages the use of equitable pricing strategies and considers that the EU should support it in some form. Health Action International and Oxfam see benefits, but note that there should be control on companies' pricing.

Médecins Sans Frontières finds generic competition preferable and therefore considered the EU should not support tiered pricing.

- *Is a regulation the most appropriate instrument for EU intervention?*

The policy aim of the Regulation was to safeguard against the diversion of low-priced pharmaceuticals destined for poor markets and prevent price erosion in developed countries' markets. An EU regulation was required to authorise customs authorities to suspend the release of, or detain, products. Otherwise, they are not empowered to seize parallel-traded medicines re-imported into the EU.

Market and legislative changes have considerably reduced the risk that was anticipated at the time the Regulation was adopted; in particular:

- companies have introduced private mechanisms to mitigate the risk of diversion. One key measure is to package products differently. According to the Access to Medicines Index, half of the companies with tiered prices for essential medicines adapt their brochures and packaging materials, also to help ensure medicine is taken correctly. Five companies do so for some products, while only three do not adapt their materials at all;²³
- the purchase by organisations such as the Global Fund, PEPFAR and UNAIDS of medicines for all of the diseases covered by the Regulation have significantly improved the security of the supply chain; and
- the EU has taken measures to protect the supply chain better against falsified medicines, notably by identifying products.

GSK noted that there remains a risk. For example, its new HIV product, dolutegravir, will be available in high volumes at low prices in low- and middle-income countries before entering the European market, potentially creating more interest in trade and a risk of diversion. As a result, it is considering registering the product under the Regulation.

The risk of diversion for malaria medicines was smaller from the outset, as the disease mainly affects low- and middle-income countries and there is no substantial market in high-income countries.

For TB products, trade diversion is generally not a concern, as the market in developed countries is not large enough to encourage it.

CRA finds that the Regulation is no longer relevant to reducing the risk of trade diversion, but retains value as a signal of Commission support for tiered pricing.

The pharmaceutical industry considers that the Regulation should not be withdrawn, as this would send the wrong signal. Most companies with HIV/AIDS medicines use tiered pricing (e.g. under the Accelerating Access Initiative) and the European Federation of Pharmaceutical Industries and Associations noted that policy should support voluntary differential pricing by companies. Industry stakeholders interviewed by CRA highlighted that the Regulation signals support for tiered pricing.

²³ Access to Medicine Index 2014, Access to Medicines Foundation.

As Médecins Sans Frontières prefers generic competition and considers that the Regulation shows Commission support for tiered pricing, it called for it to be repealed.

Other NGOs noted that tiered pricing is a tool for improving access to medicines and remains a useful option for the future; they argued that the Regulation should therefore not be scrapped without being replaced with something else.

Conclusion

- Access to medicines for all three diseases has improved, but access issues continue to merit EU intervention.
- Tiered pricing in general can still make a contribution to access to medicines.
- A regulation is no longer needed to reduce the risk of trade diversion, as the risk is largely being addressed by private action by pharmaceutical companies, better control of supply chains by aid programmes and legislation on the control of medicine supply.
- However, most stakeholders consider that the Regulation retains value as a signal of Commission support for tiered pricing.

What is the added value of the EU intervention in support of tiered pricing?

An EU regulation is required to ensure that customs prevent HIV/AIDS, TB and malaria medicines sold to the poorest developing countries at discounted prices from being re-imported into the EU. Only a regulation can authorise customs authorities to suspend the release of, or detain, parallel-traded medicines being re-imported into the EU.

As to the added value of intervention as such, the EU is committed to the WHO global strategy and plan of action, which aims *inter alia* to encourage differential pricing, partly by taking action against product diversion.

In that context, stakeholders note that the Regulation has added value as a signal of Commission support for tiered pricing. Private tiered-pricing initiatives cannot send the same signal of public support.

The most likely consequence of withdrawing the Regulation is that the Commission would be seen as retracting its support for tiered pricing.

Section 7: Overall conclusions

The Regulation was evaluated on four criteria: effectiveness, efficiency, coherence and relevance. On that basis, it can be assessed against key REFIT objectives, i.e. whether it is fit for purpose, whether it achieves its objectives at minimal cost and whether there is potential for simplification.

As regards **EU added value**, customs measures against product diversion relate to matters falling within the scope of the common commercial policy, an area in which the EU has exclusive competence under Article 207 TFEU. Only a regulation can empower customs authorities to suspend the release of, or detain, parallel-traded medicines re-imported into the EU. Therefore, there is added value in intervention at EU level.

On **effectiveness**, CRA found that the Regulation increased the supply of GSK products to the target countries between 2004 and 2008. It had no direct impact on prices. Although the volume of HIV medicines that GSK sold under the Regulation declined significantly from 2009, more medicines overall were supplied thanks to licences granted to generic manufacturers. GSK's medicines represented an important contribution to HIV treatment. In 2011, medicines sold under the Regulation and by licensees represented a year's supply for over a million people.

There is no evidence of product diversion, but it is not possible to attribute this solely to the Regulation, as GSK took additional measures to prevent diversion.

Use of the Regulation appears to have been limited; the risk of product diversion does not appear significant, as pharmaceutical companies found other ways of addressing it, the EU put more legal safeguards in place for medicine supply, PEPFAR and global institutions such as the Global Fund controlled supply chains better and the development of national programmes significantly reduced the risk of trade diversion. Some companies said that price-capping under the Regulation was one of the factors influencing their decision not to register, even though the prices of their products were below the ceilings.

The Regulation may have contributed to dialogue between stakeholders on improving access.

It is concluded that there has been a significant increase in access; although it is difficult to attribute this directly to the Regulation, it probably made a small positive contribution.

On **efficiency**, CRA found that the Regulation reduced the diversion risk slightly, but the costs were also limited. The costs of adding a logo and registering new package designs were small, around €200 000, compared with the much higher costs of other anti-diversion strategies that required regulatory approval, which run into millions of euros.

The costs incurred by the Commission pertain to the working time needed to run the scheme, i.e. around 40 person/weeks. Companies that do not use the scheme are under no legal obligation to take measures and face no additional administrative burden.

The benefits of the Regulation include an offsetting of costs, as it reduced GSK's need to use other, more costly anti-diversion processes for some products in some areas. CRA concluded that it can be assumed that the administrative costs are offset by the benefits. Furthermore, the Regulation improved transparency on the prices at which HIV, TB and malaria medicines

were sold to developing countries. Lastly, the Regulation sent a signal of support for tiered pricing.

The costs of the EU intervention are therefore proportionate to the benefits.

On *coherence*, CRA found that the Regulation is coherent with other EU policies and action, in particular legislation on medicines and trademarks, trade policy measures on customs and international customs cooperation, and the EU's international obligations and cooperation in the field of health and development. For example, the EU is committed to the WHO global strategy and plan of action, which aims *inter alia* to encourage differential pricing.

CRA concluded that the objective of encouraging greater access to medicines in the poorest developing countries remains *relevant*.

CRA's analysis of data from independent sources such as the WHO and UNAIDS showed that access to medicines for all three diseases has increased substantially since the 2000s, but that there are still patients without access. For all three diseases, the main components of MDG 6 have been achieved. However, there clearly remains a need to improve access to HIV/AIDS, TB and malaria medicines.

A regulation to reduce the risk of trade diversion can be seen as no longer necessary, as the risk is largely being addressed by private action by pharmaceutical companies, better control of supply chains by aid programmes and legislation on the control of medicine supply. For example, access to modern treatment has improved greatly through the creation of the Global Fund to fight AIDS, TB and malaria, which spends USD 3.5 billion a year on controlling these diseases in developing countries. The EU collectively contributes about 50 % of Global Fund resources and the Commission about 5 % (€370 million for 2014-2016 from the Development Cooperation Instrument and the European Development Fund).

However, the intervention as such has added value in the context of the EU's commitment to the WHO global strategy and plan of action, which aims *inter alia* to encourage differential pricing, partly by taking action against product diversion.

In that context, the Regulation has added value as a signal of EU support for tiered pricing which can prompt companies to put tiered-pricing programmes in place. However,, private-tiered pricing initiatives cannot send the same signal of public support. Stakeholders note that the Regulation adds value by signalling approval for tiered pricing. The most likely consequence of withdrawing the Regulation is that the EU would be seen as retracting its support for tiered pricing.

On the contribution tiered pricing can make, academics and stakeholders noted that it has some value today. CRA noted that other mechanisms such as voluntary licensing have their limitations and are generally complementary. They reduce the relevance of tiered pricing, but it still has a role in improving access.

The pharmaceutical industry supports tiered pricing, as it gives society improved access and allows industry to generate returns for innovation. The Access to Medicines Foundation encourages the use of advanced tiered pricing ('equitable pricing') strategies. Health Action International, Médecins Sans Frontières and Oxfam argue that tiered pricing allows for lower prices, but find generic competition preferable.

With the exception of Médecins Sans Frontières, the stakeholders expressed support for a role for the EU in support of tiered pricing and consider that the Regulation should therefore not be scrapped without being replaced with something else.

In view of these conclusions, the Regulation can be assessed against the **REFIT objectives**:

- As the objective of improving access to medicines in the poorest developing countries remains relevant, tiered pricing still has value, and as the Regulation shows EU support for tiered pricing, it is concluded that *it is still fit for purpose*.
- As the costs of using the Regulation are small compared with the other costs of putting medicines on the market and companies that do not use the scheme face no administrative burden, it is concluded that *the associated costs and burdens are minimised*.
- As the procedure for registering products under the Regulation consists of simply sending a completed form to the Commission and a logo can be added to packs as part of normal production procedures, it is concluded that *there is no further potential for simplification*.

Further action

In view of the small administrative burden, the benefits that have been realised, the added value of a signal of support for tiered pricing and its place in the overall context of action to target major diseases, the Regulation still has a role in the future in the context of the aim (stated in the *Trade for All* Communication²⁴) of continuing to promote an ambitious global health agenda and better access to medicines in poor countries.

In that context, many other measures are being taken. For example, on 6 November 2015 the WTO Council on TRIPS decided to exempt LDCs from WTO obligations to provide patent protection for pharmaceutical products to support access to medicines until at least 2033. The EU gave its full support to this measure.

Other EU action includes the global health strategy (part of the commitment to the WHO global strategy and plan of action), Commission-funded development programmes for the supply of essential medicines in developing countries and health aspects of research programmes with developing countries.

²⁴ COM/2015/0497 of 14 October 2015

Annexes

Annex 1: Procedural information

Agenda planning references: 2015/TRADE/022;

Work programme reference: CWP / 2015 / CWP2015REFIT

A steering group composed of DGs TRADE, DEVCO, EEAS, ENTR, MARKT, SANCO, TAXUD and SG was set up on 16 January 2014 and validated the evaluation mandate on 6 June 2014.

An external contractor was commissioned to gather data to evaluate the Regulation. The steering group validated the terms of reference on 6 June 2014 and these were published as call for tender No TRADE14/B3/B01, contract notice OJ 2014/S 127-225767 of 5 July 2014 (<http://ec.europa.eu/trade/trade-policy-and-you/calls-for-tender/>).

Charles River Associates (CRA) was commissioned to evaluate Council Regulation (EC) No 953/2003 as part of the Commission's regulatory fitness and performance (REFIT) programme. The contract with CRA was signed on 5 December 2014.

In line with the Commission's evaluation standards, there were four points to be considered:

- effectiveness: to what extent has the Regulation achieved its goals?
- efficiency: were the costs involved justified, given the achievements? This includes in particular an assessment of administrative burden for businesses, especially small and medium-sized enterprises;
- coherence: to what extent is the Regulation coherent internally, with other EU policies, with the objectives of the Treaty Establishing the European Community, and with the activities of other actors? and
- relevance: to what extent do the (original) objectives (still) correspond to EU needs? What is the role of a regulation?

CRA was also asked to:

- provide recommendations – based on our findings – on:
 - the continuing need for EU-level policy intervention in support of tiered-pricing schemes; and
 - the most appropriate form that any such intervention should take; and
- reach a clear conclusion on whether the existing regulatory framework should be maintained; and if so
- outline how the functioning of the Regulation could be improved.

To perform the assessment, CRA conducted an extensive literature review, evaluated the impact of the Regulation on prices and volumes, and conducted 34 interviews with companies whose products are eligible for registration under the Regulation, Commission staff, national customs authorities, NGOs, international bodies and academics.

The draft report was discussed at a public workshop on 15 July 2015.

CRA delivered its final report by 5 August, as planned. The steering group evaluated it at a meeting on 10 September and concluded that it delivered what had been agreed in the roadmap.

All documents are available at <http://ec.europa.eu/trade/policy/accessing-markets/intellectual-property/access-to-medicines/>

Annex 2: Stakeholder consultation

Process

The January 2015 roadmap involved commissioning a study from an external contractor and holding a workshop 15 July 2015 in Brussels on its provisional results. Registration for the workshop opened on the DG TRADE website on 17 June and an announcement was sent to DG TRADE's civil society dialogue mailing list. The provisional results were published on the site on 1 July 2015.²⁵ Stakeholders were invited to submit written comments by 22 July.

Given the specialised subject area of the Regulation and its limited use, it was decided that a targeted consultation would be more appropriate than an internet-based public consultation. This was announced in the roadmap.

CRA interviewed the main stakeholders in the field, including pharmaceutical industry, international and civil society organisations dealing with access to medicines, and Member State authorities, in particular those dealing with pharmaceutical products, health and trade. Interviews were also held with companies and key NGOs involved in access to medicines, academics and experts in the field.

As planned, the provisional results of the study were made available on DG TRADE's website on 1 July and discussed at a workshop on 15 July in Brussels. This was attended by 40 representatives of industry and international organisations, academics and civil society organisations dealing with access to medicines, and Member States. The aim was to test the findings of the evaluation. Three stakeholders provided written drafting comments by the 22 July deadline and these were incorporated in the report.

CRA delivered the final report taking into account the written comments and those received at the workshop by 5 August, as planned.

Summary of consultations

For the evaluation, CRA interviewed stakeholders to gather evidence and opinions on the effectiveness, efficiency, coherence and relevance of the Regulation.

This REFIT evaluation is based on CRA's study, which itself was based on feedback from the interviews, together with literature research and data analysis. The study notes stakeholders' views on the market situation and the Regulation, indicating clearly where these diverged.

CRA invited all interviewees to comment on the text of the study to ensure that it accurately reflected their input and positions. They were also invited to comment on CRA's preliminary findings and conclusions and to participate in the workshop before the report was finalised.

In order to understand how they had decided whether or not to use the Regulation, CRA interviewed nine companies producing HIV, TB or malaria products that qualified for registration under the Regulation:

- the company that registered products (GSK, subsequently ViiV);

²⁵ All documents and provisional study results are available at <http://ec.europa.eu/trade/policy/accessing-markets/intellectual-property/access-to-medicines/>.

- companies with leading HIV products, as identified in the WHO ‘preferred therapy’ list and the Medicines Patent Pool during the period in which the Regulation had been in force (Roche, Janssen, MSD, Pfizer); and
- companies with malaria and TB products on the market or in the pipeline (Novartis, Pfizer, Sanofi and Janssen).

It also interviewed:

- Commission experts, in particular in DG TRADE, DG TAXUD and DG DEVCO;
- national customs experts; and
- the main NGOs involved in tackling medicine affordability in low-income countries (Médecins Sans Frontières, Health Action International; OXFAM, the Access to Medicines Foundation and Save the Children).

Targeted interviews on the efficiency of the Regulation were held with Commission staff involved in drafting and implementing it, industry stakeholders and customs authorities. CRA also interviewed academics – Dr Andrew Hill (University of Liverpool), Dr Margaret Kyle (MINES ParisTech), Prof David G Taylor (University College London – School of Pharmacy) and Dr Prashant Yadav (WDI University of Michigan) – and international organisations (the WHO, the Global Fund and the Medicines Patent Pool).

Stakeholders expressed the following views on the contribution that tiered pricing can make to improving access to medicines:

- the academics argued that tiered pricing has a role to play in improving access to medicines, but that its use varies considerably depending, for example, on whether the same product is available on developing and EU markets;
- the NGOs expressed mixed views. Health Action International, Médecins Sans Frontières and Oxfam agreed that tiered pricing can allow for lower prices, but they find generic competition preferable; and
- the industry considers that tiered pricing leads to good results. It allows for prices that better reflect local levels of affordability, thereby allowing industry to generate returns for innovation and giving society improved access.

Stakeholders’ views on the role for EU-level policy intervention in support of tiered pricing were as follows:

- the industry interviewees and the industry association noted that policy should support voluntary differential pricing by companies;
- the academics expressed the view that tiered pricing has a role to play and that the EU should show support for it;
- the Access to Medicines Foundation encourages the use of equitable pricing strategies and considers that the EU should support it in some form. Health Action International and Oxfam see benefits, but note that there should be control on companies’ pricing; and
- Médecins Sans Frontières finds generic competition preferable and therefore considered that the EU should not support tiered pricing.

Views on the ongoing need to address the threat of diversion through a tiered-pricing Regulation were as follows:

- the industry considers that the Regulation should not be withdrawn, as this would send the wrong signal. Most companies producing HIV/AIDS medicines use tiered pricing (e.g. under the Accelerating Access Initiative) and the industry association noted that policy should support voluntary differential pricing by companies. The industry stakeholders highlighted that the Regulation signals approval of tiered pricing;
- as Médecins Sans Frontières prefers generic competition and sees the Regulation as showing Commission support for tiered pricing, it called for it to be repealed; and
- other NGOs noted that tiered pricing is a tool for improving access to medicines and remains a useful option for the future. The Regulation should therefore not be scrapped without being replaced with something else.

Annex 3: Methods and analytical models used in preparing the evaluation

Data collection by CRA

In order to establish whether there had been less trade diversion since the introduction of the Regulation, CRA looked at:

- any direct evidence of the extent of trade diversion before and afterwards; and
- whether companies had sought to remove illegally imported products.

Evidence was compiled through an academic literature and a press/media search, using internet searches on research terms such as ‘illegal import’ and ‘parallel trade into the EU’. CRA found, for example, a 2005 *Pharma Times* report that GSK had experienced trade diversion of their product Combivir.²⁶ CRA carried out a standard internet search and a search of legal databases for cases in which companies pursued trademark and patent issues to prevent re-importation into the EU; it found a number of court cases that were then analysed.

CRA reviewed all annual performance reports for the Regulation, which provide a brief background, products registered, diseases treated, volumes sold and any changes in supply. There is also an evaluation of the prices of products not covered by the Regulation and whether they meet the criteria in Article 3. CRA discussed the interpretation of data with DG TRADE staff responsible for compiling the data supplied by the manufacturer.

Lastly, CRA interviewed an expert in DG TAXUD to understand the data collected by national customs authorities. After identifying cases of diversion in Belgium and the Netherlands, CRA contacted the customs authorities and regulatory agencies there to gain a better understanding of the legislative and regulatory framework at national level.

CRA also interviewed a number of pharmaceutical companies (see below) and NGOs to hear their assessment of the extent of the problem in 2002 and subsequently.

Price, volume and affordability of products

In order to analyse the price and volume of medicines, CRA collected data from the global price reporting mechanism (GPRM), a database recording international transactions of HIV/AIDS, TB and malaria medicines purchased by national programmes in low- and middle-income countries. The information, which includes volumes, prices, international commercial terms (INCO), countries of destination and procurement dates, was queried using an end-user interface that enables the database to be searched by regimen (brand, formulation), country, income group, region and period of time. Some of the data was cross-checked against additional sources of price and volume data for HIV products, such as the Global Fund’s price and quality reporting (PQR) tool, a web-based system which contains a summary of main international reference prices and recent market data, including number and volume of transactions, unit price, total price paid and limited information on mark-ups.^{27, 28}

²⁶ Boseley, S. and Carroll, R., ‘Profiteers resell Africa’s cheap Aids drugs’, *The Guardian*, 3 October 2002.

²⁷ <http://www.theglobalfund.org/en/procurement/pqr/>

CRA calculated the affordability of products using an adapted version of the WHO/HAI methodology. It converted the minimum nominal monthly wages in local currency into annual monthly wages in US dollar terms using International Labour Organisation (ILO) and World Bank data.²⁹ The affordability index was then calculated for each drug for a given year and country by dividing annual treatment cost by annual minimum wage. The index indicates how many years of treatment with a given drug an individual can afford if paid the minimum wage. The higher the index, the more affordable the medicine.

Methodology for assessing the impact of the Regulation on prices and volume

To gauge the impact of the Regulation, CRA focused on a particular group of products (NRTIs)³⁰ and looked at the volumes and prices of products covered and not covered by the Regulation.

Simply comparing the prices of Regulation-registered products in Annex-II countries with those in OECD countries is not sufficient to draw conclusions on the effect of the Regulation on prices.

Equally, one cannot directly compare prices of products covered and not covered by the Regulation, because:

- products differ in terms of efficacy;
- products differ in terms of line of use (e.g. first-line or second-line treatments); and
- their use in combination with other products may differ.

CRA therefore considered the relative prices in Annex-II and non-Annex-II countries of products covered and not covered by the Regulation. If the Regulation had an effect on prices, one would expect the prices for registered products in Annex-II countries to be lower than those for other types of product (see Figure 1), after controlling for differences in the product or country in which it is sold.

²⁸ To ensure comparability between products and across different product strengths, CRA converted price and volumes on the basis of WHO daily defined doses (DDD). For price, it calculated the ex-factory unit price into ex-factory annual treatment costs assuming that the DDD is taken for 365 days of the year. For volumes, it converted total units sold into number of treatment days, assuming that the WHO DDD is the required daily dose. WHO, *ATC/DDD Index 2015*, http://www.whocc.no/atc_ddd_index/.

²⁹ ILOSTAT database for minimum wage and World Bank world development indicator database for the official annual exchange rate.

³⁰ Nucleoside analogue reverse-transcriptase inhibitors; only NRTIs were registered under the Regulation.

Figure 1: Framework to test hypothesis

		<u>Product type</u>	
		Registered	Not registered
<u>Country type</u>	Annex II	Regulation (e.g. Combivir sold in South Africa)	Control (e.g. Viread sold in South Africa)
	Not Annex II	Control (e.g. Combivir sold in El Salvador)	Control (e.g. Viread sold in El Salvador)

The GPRM records purchases of HIV/AIDS, TB and malaria medicines by national programmes in low- and middle-income countries. These records are provided by funders such as the Global Fund and PEPFAR, and procurement organisations such as the Global Drug Facility, the Clinton Foundation and national governments. The data is recorded on a transaction basis and includes information on pack size, strength, dosage formation, units sold, ex-factory price and purchasing country. The coverage of the GPRM has clearly changed over the period, but it remains the best source of data on sales to low- and middle-income countries and coverage issues should apply to all products (whether or not covered by the Regulation).

As each NRTI has several formulations, strengths and pack sizes, the most comparable basis for measuring price is annual treatment cost rather than price per pack or per unit. CRA calculated the annual treatment cost for each transaction using the ex-factory unit price and assuming the WHO daily defined dose for each molecule. It converted the volumes sold into a number of daily doses so that volumes were comparable across products and product strengths.

Given the number of products and countries involved, CRA used regression analysis to test whether the products covered by the Regulation perform differently from those not covered. It created a dummy variable ‘Regulation’ to distinguish these purchases of registered products by Annex-II countries. The control group are purchases that do not fall under the Regulation, i.e. registered products purchased by non-Annex II countries, non-registered products purchased by Annex-II countries and non-registered products purchased by non-Annex-II countries. CRA then analysed the effect of the Regulation on price and volumes.

GPRM data is available for 2004 onwards. Because of the rapid innovation in the field of ARVs and volumes of Regulation products fell sharply in 2009 (see section 2), CRA focused on price and volumes of NRTIs from 2004 to 2008.

Effect of Regulation on NRTI prices according to GPRM

CRA analysed all recorded purchases of originator NRTIs between 2004 and 2008 to determine the effect of the Regulation on price (see Table 1).³¹ CRA converted the cost of treatment into logs, so the dummy Regulation reflects the percentage change in price resulting from the Regulation. CRA finds that the Regulation has a negative impact, but this is not statistically significant.

Table 1: Effect of the Regulation on annual treatment costs, 2004-2008

Log of weighted average annual treatment cost	(1)	(2)
Regulation	-0.162 (0.190)	-0.152 (0.190)
Time		-0.00922 (0.0260)
Brand fixed effects	Y	Y
Country fixed effects	Y	Y
Time fixed effects	Y	
Constant	6.652*** (0.347)	6.687*** (0.340)
Observations	942	942
R-squared	0.582	0.580
Adjusted R-squared	0.525	0.524

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

³¹ WHO, *ATC/DDD Index 2015*; http://www.whocc.no/atc_ddd_index/. GPRM also provided annual treatment costs, but the daily dose on which such calculations were based had unexplained variations even within molecules of the same strength. CRA dropped purchases of the following molecule and strengths because the required units per day didn't reach the DDD 115 mg, 125 mg, 150 mg and 167 mg, and Zerit (stavudine) 15 mg.

The results are sensitive to the specification. In particular, changing the time period, including volumes (which do seem to be negatively related to price), and excluding outliers affect the scale of the impact of the Regulation. However, CRA concludes that there is no statistically significant difference between the tiered prices of products using and not using the Regulation. This is consistent with what was said in the interviews.

Effect of Regulation on NRTI volumes

CRA performed the same analysis on volumes. If the Regulation was effective, sales of registered products could be expected to be higher in Annex-II countries. CRA analysed all recorded purchases of originator NRTIs between 2004 and 2008 to determine the effect of the Regulation on volumes (see Table 2). Here, CRA finds that the Regulation had a significant positive impact, with Annex II countries purchasing 79 % greater volumes of registered originator molecules, even after controlling for differences due to brand, country and time of purchase (regression 1).

Table 2: Effect of Regulation on total daily defined doses (DDD) purchased, 2004-2008

Log of total DDD	(1)	(2)
Regulation	0.791** (0.391)	0.782** (0.390)
Time		0.243*** (0.0669)
Brand fixed effects	Y	Y
Country fixed effects	Y	Y
Time fixed effects	Y	
Constant	7.446*** (0.583)	7.301*** (0.596)
Observations	942	942
R-squared	0.477	0.474
Adjusted R-squared	0.405	0.405

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

CRA also tested whether this result was sensitive to the inclusion of other variables such as prevalence or GDP *per capita*. Prevalence has a statistically significant and positive effect on volumes purchased, whereas the country's average wealth does not. The impact of including these is to make the effect of the Regulation insignificant. However, as the regression based on country and brand fixed effects has the highest adjusted R-squared, CRA favours the regression results above. It therefore concludes that, for the period 2004-2008, volumes of registered products were higher in Annex-II countries.

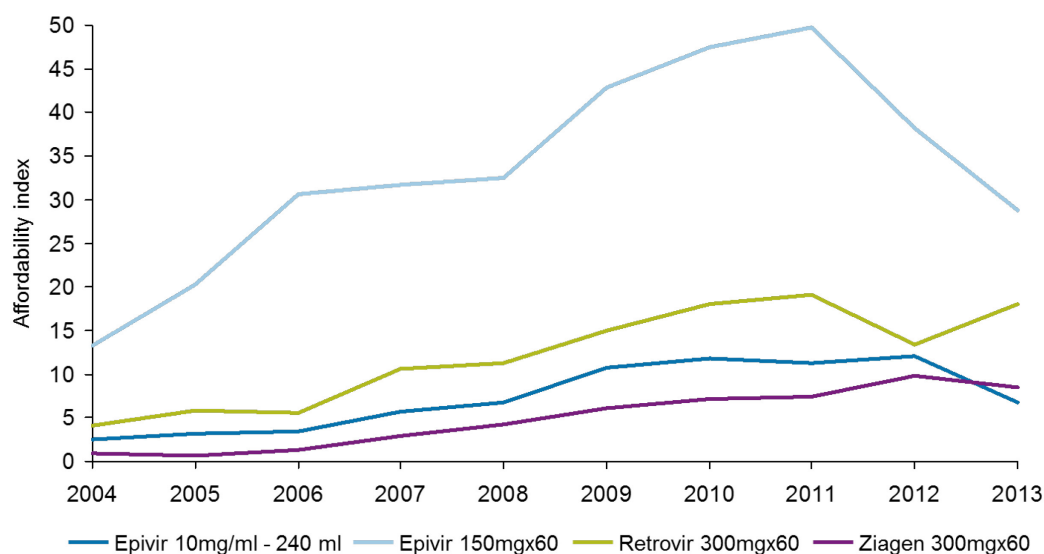
Effect of Regulation on NRTI affordability

CRA calculated the affordability index (ratio of annual minimum wage over annual treatment cost) for all Regulation drugs and non-Regulation NRTI drugs for Annex-II countries between 2004 and 2013. Annual minimum wage data was calculated as 12 times the monthly minimum wage according to ILO data converted into US dollars.

A 1:1 ratio would indicate that an individual earning the minimum wage in a particular country can afford one full year of treatment; values below one would indicate that the individual will need to work more than a year to pay for one full year of treatment; and values above one would indicate the individual would need to work less than a year to pay for one full year of treatment.

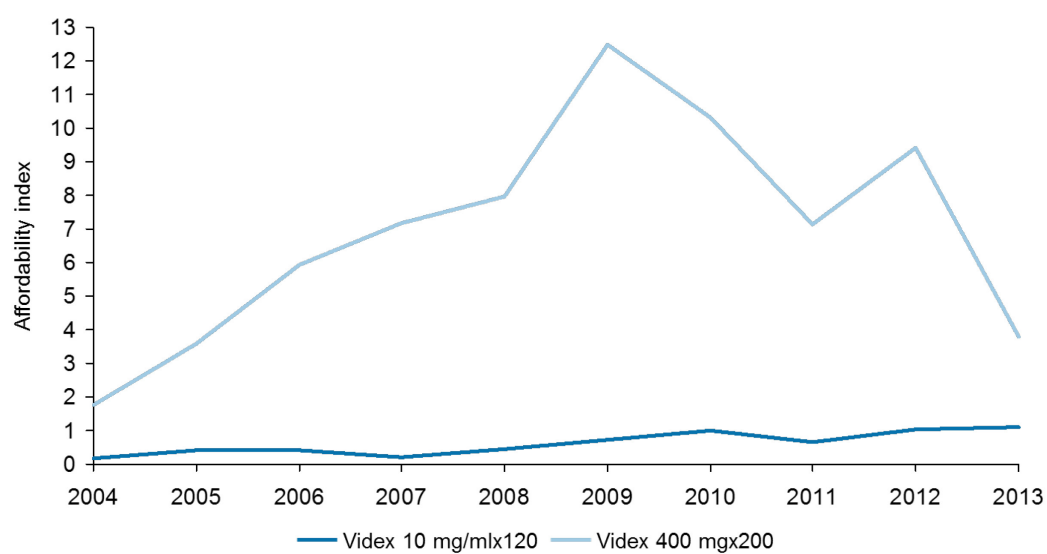
The minimum wage data had limited country and annual coverage, but it still suggests that originator NRTIs have become more affordable over the years (see Figures 2 and 3). Similarly, many changing 'environmental' factors affected the price and volume trends. However, CRA had already established (see above) that the Regulation did not have a statistically significant effect on the price of registered products in Annex-II countries. Any changes to the affordability of NRTIs would be due to factors other than the Regulation.

Figure 2: Average affordability index of Regulation drugs in Annex-II countries



Source: GPRM, ILO and WHO.

Figure 3: Average affordability index of non-Regulation NRTIs in Annex-II countries



Source: GPRM, ILO and WHO.