

Article 58 Strategic Review – Summary

Article 58 was introduced in 2004 to allow the EMA’s Committee for Medicinal Products for Human Use (CHMP), in cooperation with the World Health Organization (WHO), to give opinions on medicines and vaccines for human use that are intended exclusively for markets outside of the European Union (EU).

Article 58 aims to help address public health challenges existing in low and middle income countries (LMICs) by providing a mechanism through which scientific and manufacturing expertise could be provided to manufacturers, the WHO, NRAs from LMICs, and the broader global health community regarding development and assessment of products intended to be marketed outside the EU and in LMICs¹.

Article 58 combines EMA’s world-class scientific, clinical, and manufacturing review capabilities with the local epidemiology and disease expertise of the WHO and LMIC national regulators to provide a unique development and assessment pathway.

In 2015, the EMA, together with the European Commission and in collaboration with the Bill & Melinda Gates Foundation, carried out a strategic review of the use, role and vision of its ‘Article 58’ scientific opinion. The objective of the review was to understand the public health landscape in LMICs that Article 58 seeks to address, Article 58’s role within this ecosystem, and potential enhancements to the procedure. The review drew insights from desk research, a variety of product case studies, and 45+ stakeholder interviews across manufacturers, product development partnerships, LMIC regulators and key procurers of global health medicines. This memo summarizes the conclusions of that review, including Article 58’s use to date and a set of recommendations that would allow the EMA and the European Commission to further enhance Article 58’s public health impact.

THE USE OF ARTICLE 58 TO DATE

Since the introduction of Article 58, strong progress has been made in addressing the public health challenges of the developing world. Health systems have been improving, and meaningful progress has been made in reducing disease burdens (e.g., AIDS-related deaths have decreased by 29% since 2000, and the mortality rate from malaria has decreased by 47%²).

Article 58’s role to date has been limited, with seven³ positive opinions, predominantly driven by the fact that the pathway is applicable only to products

¹ Regulation 726/2004/EC, which also includes Article 58, introduced a “sunset” clause that provides for the rescission of EU marketing authorisation in cases where a product has not been put on the market in the EU within 3 years

² UNAIDS HIV report, WHO World Malaria Report

³ The eight positive opinion (Mosquirix) was issued shortly after this exercise was concluded

intended exclusively for use outside the EU⁴ and, furthermore, is best suited towards innovative products⁵ as opposed to Generics. These seven products have experienced mixed commercial success in the LMICs post-opinion. While over 60% of these products have been hampered by poor NRA recognition of Article 58 opinions, most of the products with positive opinion from Article 58 have suffered from poor commercial viability, unrelated to the regulatory pathway. The seven products have been:

- **Anti-Retrovirals (ARVs) such as Aluvia (Abbvie), Lamivudine (ViiV), and Lamivudine/Zidovudine (ViiV)** were differently-coloured replicas of existing EU authorized drugs and received positive Article 58 opinion in 2009-10. These versions were introduced in the LMICs to combat EU re-importation. ViiV's products are now in the process of being withdrawn
- **Hexaxim (Sanofi)** is the first Hexavalent vaccine and gained positive Article 58 opinion in 2012. While the vaccine has the potential to have significant public health impact, its success will depend on how immunization schedules evolve. It is also worth noting that following its Article 58 opinion, Sanofi realized the market potential for Hexaxim in EU and applied through EMA's central pathway to gain an EU marketing authorisation.
- **Tritanrix (GSK)**, a quadravalent vaccine (DTwP-Hep B), received its positive opinion in 2013 while being phased out globally (in favour of pentavalent vaccine adoption).
- **Hemoproston (Linepharma)**, a misoprostol treatment for postpartum haemorrhage, received a positive opinion in 2014 and has not yet been marketed
- **Pyramax (Shin Poong)**, an anti-malarial medication, has been more successful, with approvals in four core South East Asian target markets following its positive Article 58 opinion in 2014. Additionally, it has been approved in six African countries, though again it has yet to be fully launched.

While the success of Article 58 products has been limited to date, manufacturers have found the scientific advice received from EMA experts to be extremely helpful in shaping their clinical plans. This is especially true for pipeline products (such as RTS,S, Flexinidazole etc.) that have engaged with the EMA early on in their clinical development. Manufacturers have been unanimously impressed by the professionalism and rigour of CHMP's scientific assessment as well as the responsiveness of EMA co-ordinators during the process. Likewise, the few LMIC NRAs that have been experts/observers during CHMP reviews have found the experience extremely valuable.

⁴ Many products, regardless of their target disease, have some potential market in the EU: be it for travellers, healthcare workers, military, or stockpiles. Even where a manufacturer cannot foresee any value to marketing a product within the EU, often manufacturers remain reluctant to limit their options by foregoing EU marketing authorisation.

⁵ Innovative products include New Chemical or Molecular Entities, novel vaccines / biologics and known Molecular entities in trials for the first time in a new indication

Despite the appreciation by NRAs and manufacturers on the process elements of Article 58, several challenges have emerged. Low awareness by NRAs, limited mechanisms to gain faster NRA approvals post opinion, inconsistent coordination with WHO during Article 58 and manufacturer hesitance given few successful precedents are significant barriers to uptake of Article 58 today. The next section lays out detailed analyses on teasing out these challenges and options for enhancing Article 58.

VALUE PROPOSITION OF ARTICLE 58 AND BARRIERS TO USE

Since Article 58's inception, a number of alternative pathways and incentives have arisen for LMIC-targeted products (*see Exhibits 1 and 2*). Many of these pathways also offer marketing authorization for the developed market, creating a substantial added incentive. Additionally, the US FDA's tropical disease pathway offers a transferrable priority review voucher that the sponsor can use to gain accelerated review of one of its compounds in the pipeline. These vouchers have recently sold for \$245 million and \$125 million.

Against this landscape of regulatory pathways, Article 58 is primarily of interest to manufacturers of innovative, new products, because generic products can go directly to the WHO for prequalification and be processed without the need for the specialized expertise of the CHMP.

The LMIC-only focus and evolution in other regulatory pathways mean that Article 58 (within its current legislative framework) has a unique value proposition for five product categories:

- Innovative, LMIC-only products that do not qualify for the FDA priority review voucher (e.g., Chagas disease, Japanese Encephalitis, Chikungunya)
- Innovative, LMIC-only products with significant variance in benefit-risk outcomes between LMICs and high income countries that might lead to different recommended usage and labelling
- Innovative, LMIC-only products manufactured by EU-based companies that need a Certificate of Pharmaceutical Product from the EMA
- LMIC-specific versions of EU-marketed products used to combat re-importation
- Vaccines produced by manufacturers in countries with NRAs not yet considered "functional" by WHO for purposes of supporting vaccine pre-qualification applications from that country

Within these areas, Article 58 will need to address the core barriers that limit it from realising its full potential:

1. Manufacturers are unclear and unconvinced of the benefits of Article 58 in attaining swifter assessment by the NRAs in LMICs and are reluctant to use it due to the lack of successful precedents.

2. For many manufacturers, the fees associated with the pathway (particularly the annual maintenance fees) are burdensome or prohibitive.
3. Many NRAs are unaware of Article 58 or consider it a “lower grade” assessment, given that it does not confer EU marketing approval.
4. Even where positive Article 58 opinions are well accepted, the subsequent pace of national assessment is no quicker than with other SRA approvals.
5. Poor coordination between the EMA and WHO⁶ – both in terms of general logistics, the use of the collaborative procedure post-positive opinion, and the management of variations and pharmacovigilance – limits the potential impact of their collaboration for both NRAs and manufacturers.

OPTIONS FOR ENHANCING ARTICLE 58

EMA and the EC can address the barriers through multiple initiatives. Near term (~1-3 years) ‘quick’ wins such as advocacy, relationship building and operational improvements are important to establish Article 58 as a pathway of choice for the relevant product categories. Longer term initiatives (3+ years) that enhance the structural elements (such as incentives) could further broaden the reach and relevance of Article 58, creating higher public health impact.

Short term recommendations

In the short term, the following actions should be taken to address the five barriers identified above and help Article 58 reach its potential:

- **Create additional incentives for manufacturers** through:
 - Clearer communication around the potential for fee waivers and potential access to the benefits of the EMA’s orphan designation, such as early acceptance (offered by analogy under the current legislative framework)
 - Enhancements to the Article 58 review process, including clear procedures for the review of variations, renewals and label changes, as well as strengthened pharmacovigilance monitoring
 - Greater involvement of target NRAs and local/WHO experts during scientific advice to ensure clinical plans are better targeted towards end-users and LMIC
NRA feedback has been incorporated all throughout
- **Ensure faster WHO prequalification of Article 58 products** by removing barriers to simultaneous prequalification and Article 58 review for vaccines
Accelerate post-opinion NRA assessments by:

⁶ The WHO plays an integral role in the Article 58 product development and CHMP assessment process by: (i) confirming the eligibility of products for Article 58; (ii) providing internal disease area and PQ expertise; and (iii) recommending external LMIC experts and NRA observers to be included in the assessment.

- Ensuring access for all Article 58 products to the WHO’s “collaborative registration” programmes
- Expanding and enhancing the capacity building aspects of the Article 58 observer programme in order to build NRA trust in Article 58 opinions
- Working with the WHO to design back-to-back Article 58 and prequalification meetings with NRAs in London. Back-to-back meetings would allow the CHMP and WHO to answer questions more efficiently, walk NRAs through their assessments, and save on the timely logistics of hosting separate meetings
- **Refresh the Article 58 brand and messaging** for both manufacturers and NRAs, supported by clear articulation of value proposition and “success stories”. Targeted conference presentations, journal articles on revamp of Article 58 and one-on-one meetings with key NRAs would be venues for such outreach. EMA / EC should also consider holding informal CHMP meetings in Africa, facilitating relationship building with key African NRAs.
- **Develop partnerships with PDPs, procurement agencies and other stakeholders** to promote Article 58 further and embed it more firmly within the global health ecosystem. Given geographic proximity, outreach to GAVI, Global Fund, UNITAID and UNICEF on a regular basis would help in engaging the core set of procurement agencies

These short-term changes will help further enhance the impact and usage of Article 58. Analysis of the development pipeline confirms that there are up to 30 possible Article 58 candidates currently in development.

Longer term considerations

As manufacturer and NRA needs evolve in the medium to long term, and new pathways and incentives appear, the EMA and EC may wish to consider broadening the scope of Article 58 by:

- Allowing simultaneous review of a product through the EMA’s central and Article 58 pathways. Manufacturers would benefit from the advantages of the EMA central pathway (e.g., EU marketing approval) as well as the Article 58 pathway (e.g., WHO and LMIC expert involvement, and faster prequalification and NRA assessment)
- Introducing major new incentives (e.g., priority review vouchers or decreased fees on future products, or access to significant funding and strategic advice through EMA partnerships with PDPs/donor organisations etc.)

Conclusion

The short-term enhancements outlined above would create a stronger value proposition for applicants and more clearly differentiate Article 58 from alternative pathways for LMIC-targeted products. Article 58 would offer rigorous scientific and manufacturing assessment, quicker prequalification and NRA assessment timelines,

attractive financial incentives, and the involvement of WHO and local expertise from scientific advice through to NRA assessment and into the post-authorization space. Such a pathway would provide an appealing option for the 30 or so products under development, and other similar products yet to be developed, that might consider Article 58, and would enhance the impact that EMA and the European Commission can have with Article 58 on the public health challenges facing LMICs.

EXHIBIT 1 – PATHWAY COMPARISON (MEDICINES)

		Potential pathways for LMIC targeted medicines					Other SRA pathways (non-LMIC)		
		WHO PQ	EMA Article 58	EMA with orphan	FDA: PEPFAR	FDA with TD PRV	Health Canada	Swissmedic	TGA
Pathway/benefits	Products approved since inception	419 (2001)	5 (2004)	93 (2004)	184 (2004)	6 (2004)	N/A	N/A	N/A
	Time (excl. clock stops) in days	206 ¹ (full dossier) 23 ¹ (SRA approved)	210 (website) 332 ² (new product) 82 ² (product previously approved by another SRA)	210 (website), with possibility of accelerated review	Within 180 (FDA "Priority review" status) (website)	Within 180 (if FDA "Priority review" status) (website)	180-290	290-430	255 (website)
	Costs	First: free ³ Second: USD 3K Third: USD 6K Rest: USD 8K	Review: USD 314K Annual fee: USD 113K ⁴ , Potential for fee waivers and reductions exists	As for Art. 58, but with fee reductions on all aspects	Free	Free (if qualifying as an orphan drug) ANDA: USD 59k	Review: USD 15K New drug: USD 270k ⁵	Review: USD 16K New drug: USD 76K ⁶	Generic: USD 64K New chem. entity: USD 170K ⁷
	Review focus/capabilities	CMC review, limited clinical review, any specific UN procurement requirements	Full dossier review for target population	Full dossier review for EU population	Full dossier review for target population	Full dossier review for US population	Full dossier review for local population	Full dossier review for local population	Full dossier review for local population
	Access to developed world markets	None – national approvals still required	None – no marketing authorization for EU granted	EU marketing exclusivity for 10 years	US market access (after innovator loss of exclusivity)	US market access (after innovator loss of exclusivity)	Canada	Switzerland	Australia
	Donors' use of pathway as criteria for purchase	Access to PEPFAR, GF, GDF, UNITAID markets ⁸	Access to PEPFAR ⁹ , GF, GDF, UNITAID markets ⁷	Access to PEPFAR ⁹ , GF, GDF, UNITAID markets ⁸	Access to PEPFAR, GF, GDF, UNITAID markets ⁸	Access to GF, GDF and UNITAID for malaria and TB	Access to PEPFAR ⁹ , GF, GDF, UNITAID markets ⁸	Access to PEPFAR ⁹ , GF, GDF, UNITAID markets ⁸	Access to PEPFAR ⁹ , GF, GDF, UNITAID markets ⁸
	LMIC Registration	90 day approval through collaborative registration	CPP recognized, but misconceptions exist No expedited reg.	CPP recognised; Access to collab. reg. after PQ	CPP recognised, but no known expedited registration	CPP recognised; Access to collab. reg. after PQ	CPP recognised, but no known expedited reg.	CPP recognised, but no known expedited reg.	CPP recognised, but no known expedited reg.
	Other incentives	<ul style="list-style-type: none"> Accelerated variation approvals 	<ul style="list-style-type: none"> Fast-track WHO PQ approval Automatic PQ listing 	<ul style="list-style-type: none"> Protocol/marketing assistance Fee reduction: Member state incentives Fast-track WHO PQ 	<ul style="list-style-type: none"> Fast-track WHO PQ approval Automatic PQ listing 	<ul style="list-style-type: none"> Fast-track WHO PQ Tax credit¹⁰ Priority review voucher (last sold for ~USD 260m) 	<ul style="list-style-type: none"> Fast-track WHO PQ approval 	<ul style="list-style-type: none"> Fast-track WHO PQ approval 	<ul style="list-style-type: none"> Fast-track WHO PQ approval

1 From submission to completion; 2 Average time from submission to opinion; 4 NB: Changes to WHO PQ funding and fees underway; 4 EUR 1 = USD 1.132; 5 CAD 1 = USD 0.82; 6 CHF 1 = USD 1.08; 7 AUD 1 = USD 1.30; 8 Market Size ~USD 750m; 9 Excluding ARVs, which require tentative approval from FDA; 10 50% of clinical investigation costs for US companies paying tax to US government

EXHIBIT 2 – PATHWAY COMPARISON (VACCINES)

		Pathways targeted at LMICs				Other SRA pathways (non-LMIC)		
		WHO PQ	EMA Article 58	EMA central	FDA TD PRV	Health Canada	Swissmedic	TGA
Pathway benefits	Products Approved	129 ¹ (1987)	3 (2004)	25 ¹ (1995)	0 (2004)	N/A	N/A	N/A
	Time (excl. clock stops)	~300 days (website)	248 ³ days (new vaccine) 79 ³ days (vaccine previously approved by another SRA)	210 days	Within 180 days (if FDA "Priority review" status) (website)	180-290 days	290-430 days	255 days
	Costs	Review: USD 25K-66.5K Annual fee: USD 9.6-16.8K	Review: USD 314K Annual fee: USD 113K ⁴ , Potential for fee waivers and reductions exists	Review: USD 314K Annual fee: USD 113K ⁴	Free (if qualifying as an orphan disease)	USD 270K ⁵	USD 76K ⁶	USD 76K ⁶
	Review focus/capabilities	CMC review only, lack capability for clinical review	Full dossier review for target population	Full dossier review for local population	Full dossier review for local population	Full dossier review for local population	Full dossier review for local population	Full dossier review for local population
	Access to developed world markets	None – national approvals still required	None – no marketing authorization for EU granted	EU market access	US market access (after innovator loss of exclusivity)	Canada	Switzerland	Switzerland
	Donors' use of pathway as criteria for purchase	Access to PAHO, UNICEF SD and GAVI markets	Second priority access to PAHO (behind WHO PQ)	Second priority access to PAHO (behind WHO PQ)	Second priority access to PAHO (behind WHO PQ)	Second priority access to PAHO (behind WHO PQ) only	No donor access	No donor access
	LMIC Registration	90 day approval with collaborative registration	Access to collaborative reg. post-PQ	Access to collaborative reg. post-PQ	Access to collaborative reg. post-PQ	No known expedited registration	No known expedited registration	No known expedited registration
	Other incentives		Parallel PQ and Art. 58 review		Priority review voucher: ~USD 260K			

1 As of 2013; 2 Flu: 20, Hexa: 5; 3 Average time from submission to opinion; 4 EUR 1 = USD 1.13; 5 CAD 1 = USD 0.82; 6 CHF 1 = USD 1.08