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Defining the strategic vision for the EMA ‘Article 58’ process

Final read-out

September 2015

Executive summary (1/2)

- 'Article 58' was introduced to expand low and middle income country (LMIC) access to medicinal products and improve public health
- While there have been substantial gains in public health in LMICs, few innovative products seeking regulatory approval have targeted LMICs only, meaning in part that 'Article 58' has been little used
- Among the 7 products that have gone through 'Article 58', **participants appreciated the rigor and quality of the process**
  - The few **NRA observers to 'Article 58' have immensely benefited from capacity building** aspects
  - **Manufacturers who have gone through 'Article 58' appreciate the scientific advice to shape their clinical plans**, the responsiveness of EMA during the process and the technical/scientific rigor of the review
- However, other factors have contributed to the limited use of 'Article 58'
  - Alternative pathways and incentives have sprung up (e.g., FDA priority review voucher and significant fee waivers)
  - **Five core barriers to 'Article 58' realising its full potential**:
    1. **Manufacturers are unclear/unconvinced of its benefits**, and are reluctant to use it due to the lack of successful precedents
    2. For many manufacturers, the **fees are burdensome or prohibitive** (particularly the annual maintenance fees)
    3. Many **NRAs are unaware of 'Article 58' or consider it a lower grade review**, given it does not confer EU marketing approval
    4. Even where opinions are well accepted, the **pace of national assessment is no quicker** than with other SRA approvals
    5. **Poor coordination between the EMA and WHO** – both in terms of general logistics, and the management of variations and pharmacovigilance – limits the potential impact of their collaboration for both NRAs and manufacturers.
- Today there are **only a few areas where manufacturers find 'Article 58' distinctive** for LMIC-only products:
  - Innovative, LMIC-only products that do not qualify for the FDA priority review voucher (e.g., sleeping sickness medications)
  - Innovative, LMIC-only products with significant variance in benefit-risk outcomes between LMICs and high income countries (to the extent that other stringent regulatory authority (SRA) approvals might not be attainable)
  - Innovative, LMIC-only products manufactured by EU-based companies that need a CPP from the EMA
  - LMIC-specific versions of products used to combat re-importation
  - Vaccines produced by manufacturers based in countries with non-functional NRAs

Executive summary (2/2)

- There are a number of **near term enhancements** that could be put in place that could enhance 'Article 58' within these focused areas:
  - **Create additional incentives for manufacturers** through:
    - Clearer fee waivers and access to orphan designation benefits (offered by analogy under the current legislative framework)
    - Enhancements to the review process, including clear procedures for variations, renewals,label changes, and PV monitoring
    - Greater involvement of target NRAs and local/WHO experts during scientific advice
  - **Ensure faster PQ** of 'Article 58' products by removing barriers to simultaneous review of vaccines and enabling parallel PQ of drugs
  - **Accelerate post-opinion NRA assessments** by:
    - Ensuring access for all 'Article 58' products to the WHO's "collaborative registration" programme
    - Expanding and enhancing the capacity building aspects of the 'Article 58' observer programme to build trust in 'Article 58' opinions
    - Working with WHO to design back-to-back 'Article 58' and PQ meetings with NRAs in London. Joint meetings would allow CHMP and WHO to answer questions more efficiently, walk NRAs through their assessments, and save hosting separate meetings
  - **Refresh the 'Article 58' brand and messaging** for both manufacturers and NRAs, and promote the pathway through one-on-one meetings, targeted conference presentations and journal articles
  - **Develop partnerships with PDPs, procurement agencies and other stakeholders** to promote 'Article 58' further and embed it more firmly within the global health ecosystem
- Additionally, as manufacturer and NRA needs evolve, and new pathways and incentives appear, the EMA may wish to consider **possibly broadening the scope of 'Article 58' in the longer term** 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 access to significant funding and strategic advice through EMA partnerships with PDPs/donor organisations etc.)
  - Developing a new, **collaborative review process directly with NRAs**, whereby either reviews are conducted jointly with NRAs, or 'Article 58' assessment reports are shared with NRAs that will commit to national assessment within an abbreviated timeframe

Contents

Overview of the context and purpose of this review

Overall context

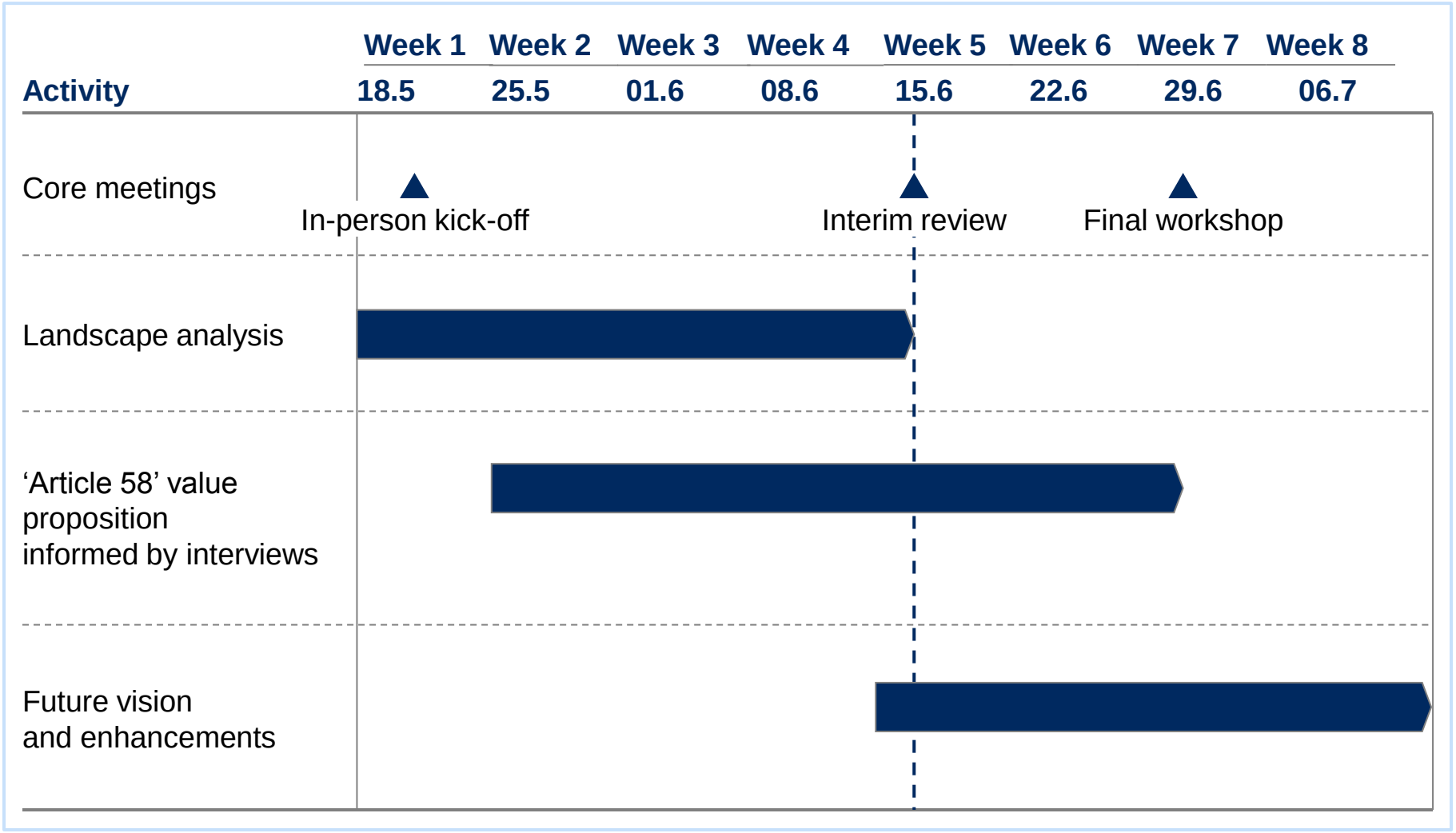
- Article 58 was introduced to help address public health challenges in LMICs – however only 7[1] products have received positive opinion so far

Purpose of the review

- Understand in more detail
  - Public health landscape in LMICs that Article 58 seeks to address
  - Article 58's role in the broader context of regulatory systems for public health
  - Value proposition and potential enhancements to the procedure

1 The 8'th product, Mosquirix, received scientific opinion shortly after this review

Overall project timeline and work-streams



Key sources of insight

Targeted research	▪ **Landscape analysis** of LMIC context to determine influence on regulatory pathways (e.g., disease burdens, regional nuances, market attractiveness) ▪ **Comparison of regulatory pathways** and their key value proposition *(complemented further by interviews)*
Interviews	▪ **48 interviews** with internal and external stakeholders focusing on 'Article 58's value proposition, its role in LMIC regulatory context, and improvement opportunities ▪ "Internal" interview partners have included: – Bill and Melinda Gates Foundation – European Commission – EMA – WHO ▪ External interview partners have included: – Manufacturers that have gone through 'Article 58' – Manufacturers that chose alternative pathways – LMIC NRAs – Global donors/procurers – PDPs
Case studies	▪ **~25 case studies**, based on desk research and interviews, to develop and test our hypotheses on: – Pathways best suited for various product types – Rationale for manufacturer/products that chose 'Article 58' vs those that did not

45+ stakeholder interviews conducted

Manufacturers (13)

Other (1)

IAVI

PDPs (3)

DNDi

PATH

MMV

Donors / procurers (3)

Global Fund

GAVI

UNFPA

NRAs (6)

DRC

Tanzania

Burkina Faso

Ghana

NEPAD

Indonesia

BMGF (6)

EMA (5)

SANTE (4)

WHO (7)

Contents

Summary of 'Article 58' review

- **While there has been great progress against the original intent of 'Article 58' – greater access to medicines and vaccines in LMICs for public health benefit – only 7 products have gone through 'Article 58' itself**
- **'Article 58's limited usage is partly due to the fact that only a few products have been developed for LMIC-only applications**
- **The 7 products that have gone through 'Article 58' have had mixed success to date:**
  - 3 of the 7 products (Aluvia, Lamivudine ViiV, Lamivudine/Zidovudine ViiV) have been coloured replicas of existing drugs to combat re-importation, with ViiV's products now being withdrawn
  - Hemaprostol has faced issues with low awareness of the Article 58 procedure with target country regulators
  - Pyramax has been partially successful with approvals in 4 South East Asian target markets[1] and 6 African markets
  - Of the two vaccine, Tritanix received an opinion while being being phased out globally (with high adoption of Penta) while the other, Hexaxim, looks promising and its adoption/impact is yet to be proven as immunization schedules evolve
- While 'participating' manufacturers have appreciated the **high-quality scientific advice**, EMA's **responsiveness** during the process and the **stringency** of the review, several **challenges have limited the further use of the pathway**

1. **Alternative pathways have sprung up** (e.g., FDA TD PRV) that provide innovators meaningful incentives (e.g., Priority Review Voucher with high resale value)
   - 5 of the 6 manufacturers to have used 'Article 58' felt they had no alternative
2. **Limited success of several 'Article 58' products in gaining easy LMIC registration** driven by:
   - Low (though improving) **awareness among regulators** (especially South East Asia and Latin America)
   - **Misconception of some regulators** around "double standard" of process due to lack of EU market approval
   - **Participation of only few NRAs** during review (who deeply appreciate its inherent capacity building aspect) and **no mechanisms to facilitate NRA registration post an 'Article 58' opinion**
3. Manufacturers that have not used the pathway are reticent to do so due to **a lack of successful precedents and uncertainty surrounding the benefits**
4. **Unclear engagement and role** of WHO (PQ/disease areas) in the process
5. **Cost of procedure** (both initial and recurring) are prohibitive for smaller manufacturers

1 Low endemic settings with Artmesinin resistance

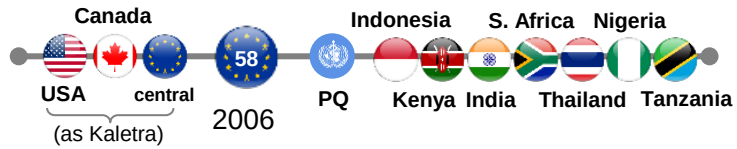
Article 58's role to tackle these public health challenges has been limited to date as it has issued only seven positive opinions[2]

Medicinal product	Reasons for using 'Article 58'	Commercial and NRA approval success
Lamivudine ViiV, Lamivudine/ Zidovudine ViiV *(ViiV)*	• **LMIC-only versions (red pills)** of EMA approved products (Epivir and Combivir) released for LMIC markets to **fight re-importation** • 'Article 58' an "administrative" step to gain approval for the chemically and clinically identical new versions	• Pre-'Article 58', Epivir and Combivir had been approved in numerous LMICs • Recently, ViiV has recently withdrawn both products from LMICs
Aluvia *(Abbvie)*	• **LMIC-only versions (red pills)** of original, EMA approved, product Kaletra released for LMIC markets **to fight re-importation**	• Launched as red LMIC version of Kaletra • Post-'Article 58' approvals in a number of LMICs • Prior to 'Article 58' approval, Kaletra approved by FDA, EMA and Health Canada
Pyramax *(Shin Poong)*	• **Chose 'Article 58' to get automatic PQ** • ***[REDACTED – COMMERCIAL CONFIDENTIAL]***	• Product applicable only in South East Asian markets with artemisinin-resistant *P. falciparum* malaria • Local approval in Vietnam, Cambodia, South Korea and Myanmar, but also Chad, Gabon, Burkina Faso, Cote d'Ivoire, Guinea, Mozambique (contrary to opinion) • Lack of inclusion in WHO STG contributing to difficulties
Hemoprostol *(Linepharma)*	• **Unable to market product in EU** since the oral medication is not appropriate for EU context, given current SOC[1] (IV oxytocin) • However, due to limitations of LMIC healthcare setting (syringes, refrigeration), the **benefit-risk assessment supports marketing of the product in LMICs**	• Discussions with NRAs have begun (with NRAs displaying poor awareness of 'Article 58')
Hexaxim *(Sanofi)*	• **Initially targeted at LMICs only** • **Manufactured in the EU,** so required Article 58 to gain a CPP that would not lapse due to sunset clause	• Following 'Article 58' at the end of 2012, received South African approval in 2013, and PQ in 2014
Tritanrix HB *(GSK)*	• **Originally marketed in EU and LMICs**, with EMA central approval, but withdrawn from EU due to EU switch from wP (whole-cell) to aP (acellular) vaccines • **Original EMA approval lapsed** due to sunset clause and GSK reapplied to 'Article 58' to maintain its CPP to allow it to continue selling in LMICs	• Received WHO PQ in 2003, and approved in Thailand, India, South Africa, Kenya before receiving an 'Article 58' positive opinion in 2013

1 Standard of Care 2 Does not include Mosquirix which was approved shortly after this work was carried out

Subsequent approvals have varied considerably due to regulatory requirements and prior versions

PRELIMINARY

Medicinal product	Description	Approvals obtained
Lamivudine ViiV, Lamivudine/ Zidovudine ViiV *(ViiV)*	▪ Both products held previous approvals as Combivir and Epivir in most core countries (including Thailand, India, South Africa, Kenya, Nigeria) ▪ Most LMICs approved the different coloured pills as Epivir and Combivir without additional review	
Aluvia *(Abbvie)*	▪ Before 'Article 58', the identical drug Kaletra had already obtained core SRAs (FDA, Health Canada, EMA central) ▪ After 'Article 58', Aluvia granted approval in many important LMICs	
Pyramax *(Shin Poong)*	▪ Positive 'Article 58' opinion in 2012 for low transmission settings with ART resistance ▪ Subsequently approved in Vietnam and Cambodia ▪ Under review in a number of other LMICs – including some that may be high endemic settings	
Hemoprostol *(Linepharma)*	▪ Linepharma has struggled with 'Article 58' awareness with LMIC regulators ▪ Linepharma has not yet launched Hemoprostol in any LMIC	
Hexaxim *(Sanofi)*	▪ Following 'Article 58' approval, South African approval granted ▪ EMA granted central marketing approval in 2013 following new decision to market in Europe ▪ PQ granted in 2014	
Tritanrix HB *(GSK)*	▪ Tritanrix HB had prior EMA central approval upon which PQ had been granted ▪ 'Article 58' opinion sought after cancellation of EMA approval due to sunset clause ▪ LMIC approvals gained pre-'Article 58' opinion	

Stakeholders shared several positive experiences about Article 58

Findings	Example quotations
1 **Manufacturers and procurers approve of the concept of a review that incorporates the expertise of an SRA, the WHO and local NRAs**	"***The fact that it includes the WHO and the NRAs is ideal***… *It should be fast and is one of the best for capacity building*… *I hope this used more, as* ***this is ideal for patients in need***."
2 **The scientific advice (both from the EMA and WHO/country experts involved) is of high quality, pragmatic and valuable in shaping clinical development plans**	"*With the EMA, there was room to discuss our concerns and issues.* ***This was very useful and immensely valuable.*** *The FDA is more likely to dismiss a package that doesn't meet a standard set of criteria*"
3 **Manufacturers and procurers find the quality and stringency of the 'Article 58' review to be at par with the EMA central pathway and they value the WHO's involvement to facilitate a quick PQ**	"***Very robust and complete assessment***… *brought in local expertise and scientific expertise… reviewed to same EMA standard.*" "We as a procurer ***don't treat it [Article 58] any differently from a central EMA approval****, but we've had very little exposure to it*" "*Absolutely to the same standard as the full EMA approval.* ***No cutting corners***."
4 **The EMA's responsiveness and process management is exceptional and highly appreciated by manufacturers**	"***The team that ran the process were really, really helpful.*** *We had lots of calls to help streamline the process and work out how to do it.*" "*We have had the same manager throughout, the* ***responsiveness has been absolutely exemplary***"
5 **NRA observers have found involvement in the 'Article 58' process to be valuable in helping their local review and in building capabilities**	"*For us, the process was beautiful – it was very interesting to follow the clinical review.* ***We are not as strong in this area, and so collaborating with EMA in this way has been great***." **- Africa** "*I find my participation in the 'Article 58' process, and the information I get,* ***very useful to me in writing guidelines***" **- Africa**

Important challenges remain to be addressed

- **Alternative pathways** (e.g., FDA TD PRV) that provide innovators meaningful incentives (e.g., Priority Review Voucher with high resale value)
- **Lack of successful precedents when manufacturers so far had limited success of several 'Article 58' products in gaining easy LMIC registration** driven by:
  - Low (though improving) **awareness and acceptance among LMIC regulators** (except those individuals within African NRAs that have been directly involved as observers)
  - **Misconception of some regulators** around "double standard" of process due to lack of EU market approval
  - **Participation of only few NRAs** during review limiting the potential of faster downstream country registrations due to "familiarity" with the particular application under review
  - **No mechanisms to facilitate and accelerate NRA registration post an 'Article 58' opinion**
- **Unclear engagement and role** of WHO (PQ vs. disease areas / programs) in the process as well as coordination issues in the process (e.g., redundant vaccine Prequalification times post Article 58, access to collaborative registration procedure)
- **Cost of procedure** (both initial and recurring) prohibitive for smaller manufacturers

Contents

Our approach to understanding the role of ‘Article 58’ in the context of other regulatory pathways

Product segmentation

- Segmented products into
  - Innovative vs established
  - Targeted at LMIC only or both LMIC and HIC

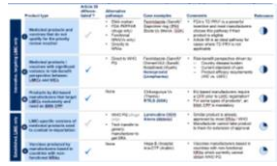
Definition of alternative pathways and relevance

- For each segment, laid out the alternative pathways and assessed relevance

Pressure testing with examples

- Pressure tested the hypotheses on where ‘Article 58’ is applicable and differentiated through 24 case studies
- Chose case studies based on pipeline analysis and key product launches in past years

Definition of product types ‘Article 58’ is applicable for



- Defined 5 product groups for which ‘Article 58’ is applicable and assessed whether there are alternative pathways for each

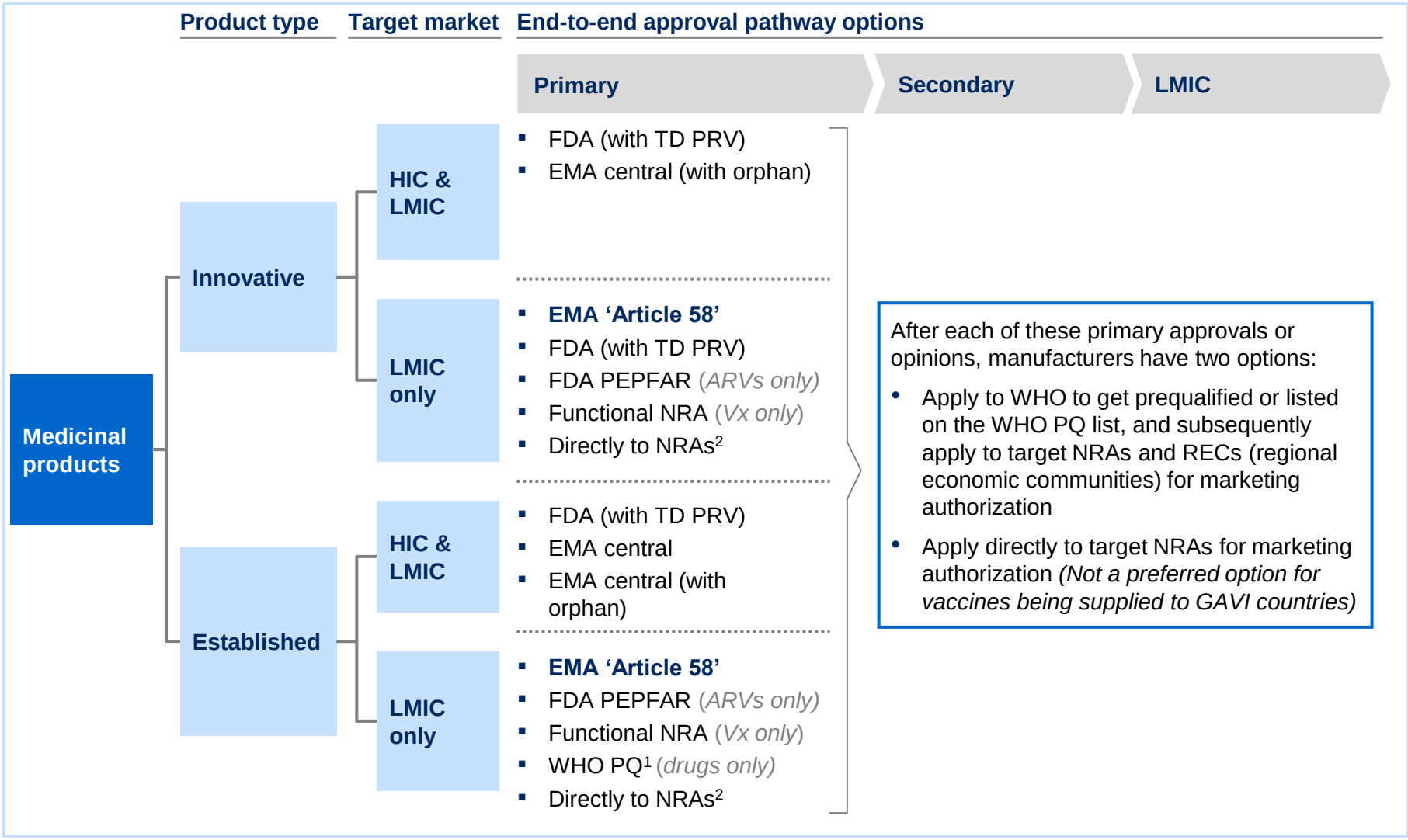
Pathway comparison

- Compared potential pathways along several criteria

Medicinal products can be classified either as innovative or established, or by reference to their target market

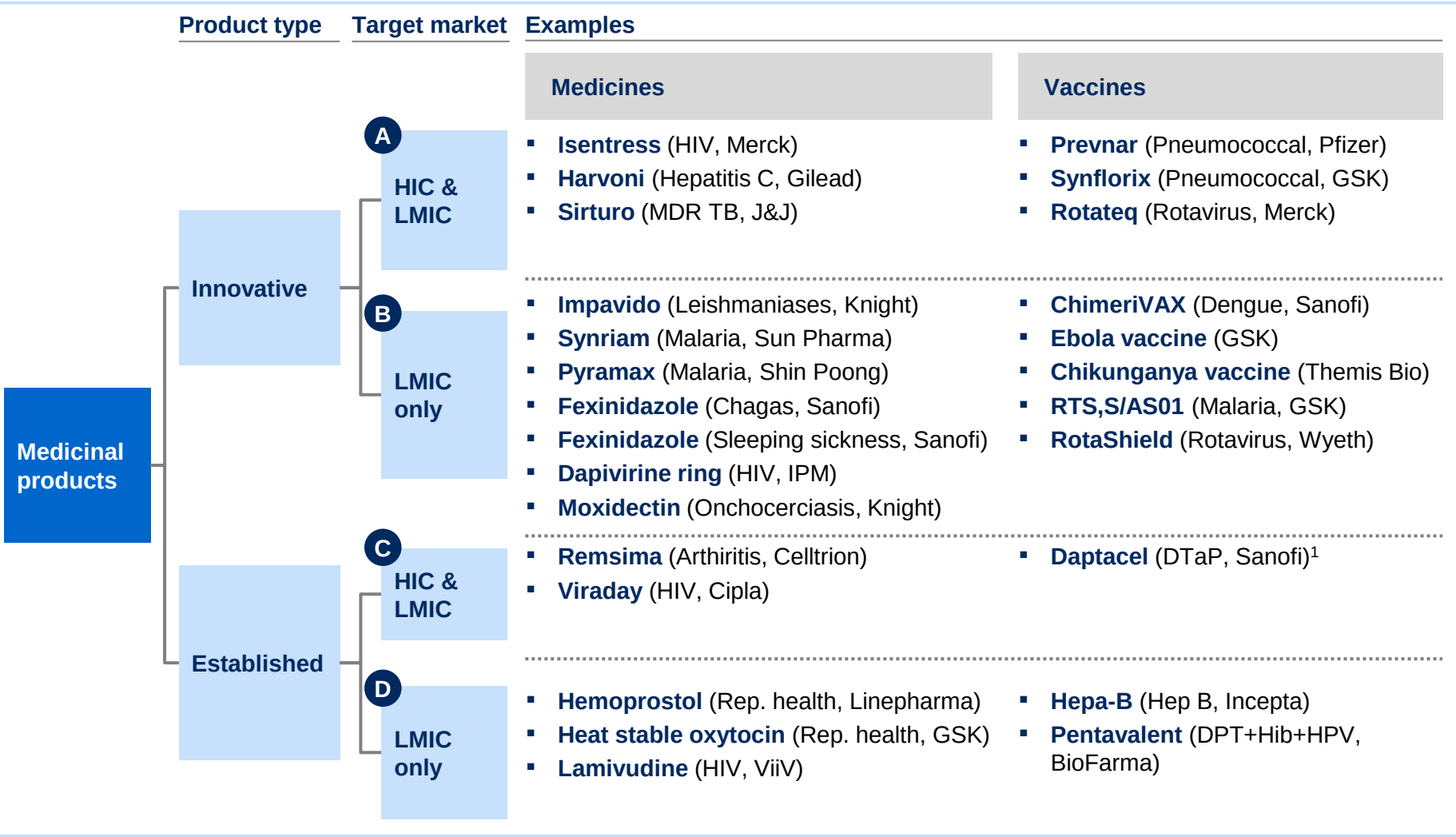
		Definition
Product type	**Innovative**	▪ **Drugs:** New molecular entities, or existing molecular entities being targeted at new indications. Dossier review will include assessment of clinical and non-clinical trials ▪ **Vaccines:** New biological entities
	Established	▪ **Drugs:** Generic molecules, new formulations of existing products and new fixed dose combinations of existing APIs. Dossier reviews will primarily revolve around CMC and bioequivalence assessment ▪ **Vaccines:** Follow-on vaccines
Target market	**LMIC and HIC**	▪ The manufacturer is targeting both LMIC and HIC markets ▪ Either may be the primary target, so long as some sales are expected in the other
	LMIC only	▪ The product is applicable to, or intended for, LMICs alone ▪ Examples include: prevention of re-importation, or if the product is not the standard of care in HICs

There are a number of different potential pathways, depending on the product type and target market



1 Where seeking donor funds for TAs serviced by WHO PQ; 2 Using the CPP and Marketing Authorization from their country of manufacture

In assessing potential products/settings that 'Article 58' might serve, we reviewed a number of case studies in each branch



1 Also marketed as Adacel, D.T.COQ/DTP in some regions, it is for whole cell pertussis and not acellular pertussis

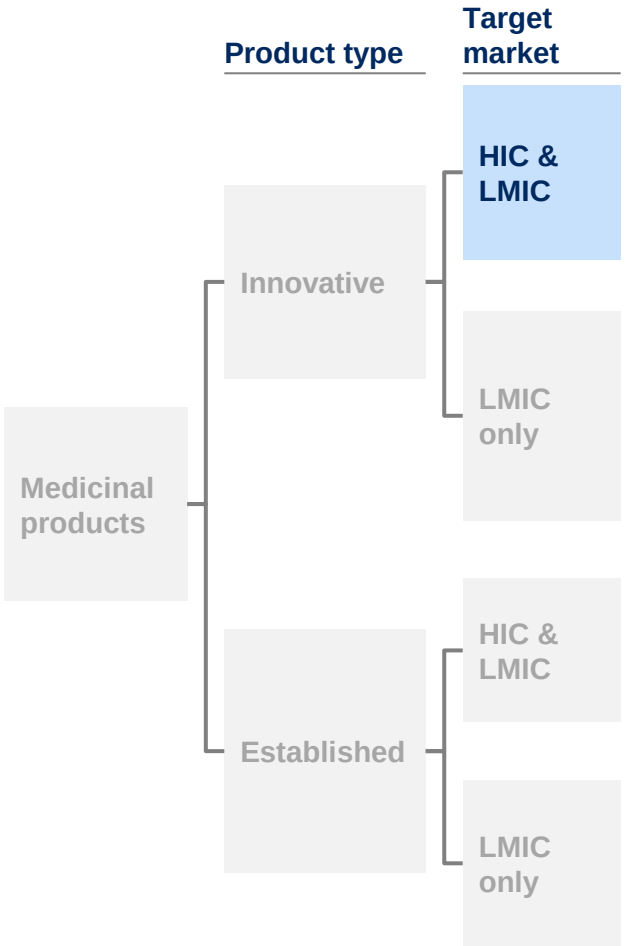
A Overview of innovative medicinal products targeted at LMICs and HICs

	Product name (INN)	Indication	Manufacturer	SRA/PQ	LMIC approvals[1]	Reg. pathway rationale
Drugs	**Harvoni** (ledipasvir, sofosbuvir)	Chronic hepatitis C (CHC) genotype 1 infection in adults	Gilead Sciences	FDA: 10/2014 EMA: 11/2014 Swiss: 12/2014 HC: 10/2014	Mongolia: 05/2015 Thailand: submitted Egypt: submitted	▪ Primary markets in HICs ▪ LMICs to be addressed via license agreements to generic manufacturers
	Isentress (raltegravir)	HIV-1 infection in patients 4 weeks of age and older	Merck & Co	FDA: 10/2007 EMA: 12/2007 Swiss: 02/2008 HC: 11/2007	Brazil, Burkina Faso, DRC: 2008 Kenya, Tanz: 2009 Ethiopia, India: 2010 Thailand: 2012 Ghana: 2013	▪ Primary markets in HICs ▪ LMICs to be addressed via license agreements to generic manufacturers
	Sirturo (bedaquiline)	Tuberculosis, Multidrug-Resistant	J&J	FDA (orphan): 12/2012 EMA (orphan): 03/2014	Thailand: submitted S. Africa: submitted	▪ Followed FDA TD PRV pathway and received priority review voucher ▪ Potential sales in HICs also
Vaccines	**Prevnar 13** (pneumococcal polysaccharide conjugate vaccine 13-valent, adsorbed)	Pneumococcal infections immunization	Pfizer	FDA: 02/2010 EMA: 12/2009 Swiss: 08/2010 PQ: 08/2010 HC: 03/2010	India: 03/2010	▪ Large markets in HICs as well as LMICs (through GAVI AMC)
	Rotateq (rotavirus vaccine, live, oral)	Rotavirus infections immunization	Merck & Co	FDA: 02/2006 EMA: 06/2006 HC: 10/2006 PQ: 10/2008	India: 04/2010	▪ Primary markets in both HICs and LMICs
	Synflorix (pneumococcal polysaccharide)	Pneumococcal infections immunization	GSK	EMA: 03/2009 PQ: 03/2010	India: 04/2011	▪ Large markets in HICs as well as LMICs (through GAVI AMC)

1 non-exhaustive

SOURCE: WHO, EMA, FDA, Health Canada, Swissmedic, country local drug agencies

A Implications for 'Article 58' from medicinal products targeted at HICs and LMICs



Implications for 'Article 58'

Innovative products targeted at HICs and LMICs are not suited for Article 58 in its current form

- Products in this category mostly target either:
  - **Predominantly diseases of affluence** that also affect LMICs (e.g., diabetes, cancer); or
  - Diseases with **majority burden in LMICs, but a small, yet meaningful, market (by value) in HICs** (e.g., HIV, Hepatitis C, Pneumococcal infections)
- Given the relevance of HIC markets, these **products/manufacturers go through the FDA central or EMA central pathway**, as 'Article 58' prohibits European sales
- Some of these products **may also qualify for orphan designation** which provides additional benefits:
  - EMA: Fee reductions, extended market exclusivity, potential accelerated review
  - FDA: Total fee waiver, extended market exclusivity, accelerated review, as well as the possibility of a priority review voucher (where product targets a tropical disease)
- **Once central US/EU approval has been granted, 'Article 58' offers no added benefit**, as manufacturers can either:
  - Go to WHO PQ, especially if targeting donor-funded markets (mostly Africa)
  - Go direct to NRAs with CPP from EU/FDA (especially if targeting Asia/Latam)

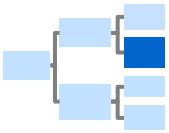
B Overview of innovative medicinal products targeted at LMICs only

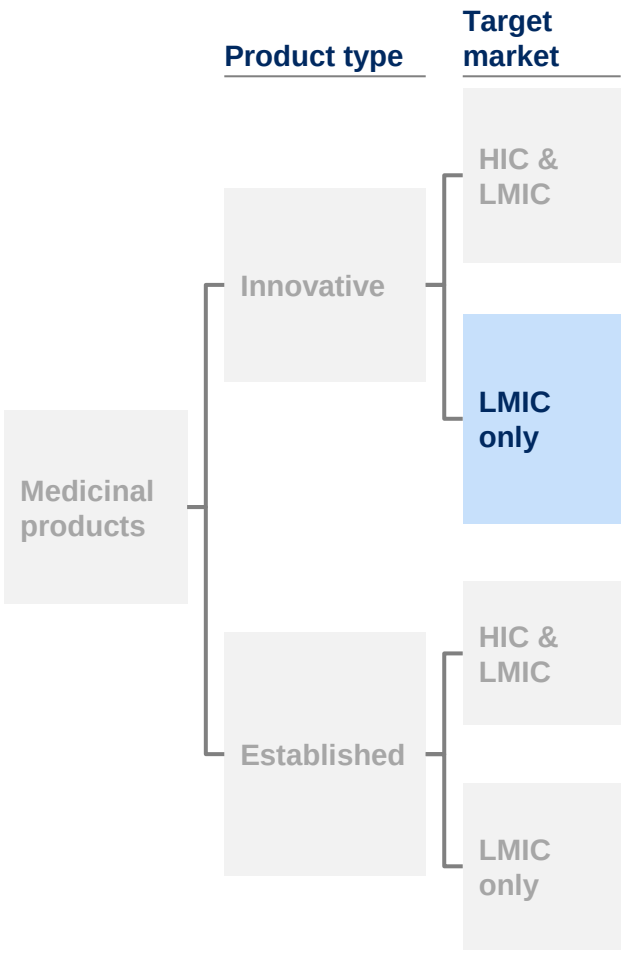
P Pipeline

	Product name (INN)	Indication	Manufacturer	SRA/PQ	LMIC approvals[1]	Approvals rationale
Drugs	**Impavido** (miltefosine)	Visc. leishmaniasis after failure of standard therapy	Knight Therapeutics	FDA: 05/2014	Molecule approved in Germany, India and UK in 2002	▪ Priority review voucher worth significantly more than drug sales ▪ Target market was HICs only
	Pyramax (pyronaridine artesunate)	*P. falciparum* (uncomplicated) & *P. vivax* malaria	Shin Poong Pharma	Art 58: 02/2012 PQ: 05/2012	Vietnam: 01/2014 Cambodia: 10/2014	▪ Target market was LMICs only
	Synriam (arterolane maleate/ piperaquine phosphate)	Acute, uncomplicated *P. falciparum* malaria	Ranbaxy (Sun)	None	India: 10/2011 9 African LMICs incl. Kenya, Nigeria: 2014	▪ Used CDSCO approval to go direct to countries with private markets for malaria medicines[2]
	Moxidectin	Onchocerciases	Medicines Dev. Int'l	P2/3 in Africa		▪ Potential candidate for EMA Art. 58
	Dapivirine Ring P	HIV pre-exposure prophylaxis	IPM/Janssen	P3 in Africa		▪ *Potential candidate for EMA Article 58 given the target market*
	Fexinidazole P	Human African Trypanosomiasis, Chagas disease	Sanofi / DnDi	P3 trial (DRC) P2 PoC trial (Bolivia)		▪ *Potential candidate for EMA Article 58 given the target market and regional concentration of disease*
Vaccines	**ChimeriVAX** (Live attenuated tetravalent)	Dengue	Sanofi	Submissions ongoing	Submitted in select Asian and Latam countries	▪ *Potential candidate for EMA Article 58 given the target market, and risk/ benefit difference in HICs*
	RotaShield (rotavirus vaccine)	Gastroenteritis due to rotavirus	Wyeth, now Pfizer	FDA: 01/1998 EMA: 07/1999	None	▪ Used FDA central pathway ▪ Discontinued due to safety concerns ▪ Risk/benefit still favourable for LMICs
	RTS,S/AS01 P	Malaria	GSK	Under Review		▪ Under Review Article 58
	Ebola vaccine P	Ebola	GSK; Merck[3]	P3 trials in Guinea		▪ *Potential candidate for EMA Article 58 given the target market*
	Chikunganya vaccine P	Chikunganya	Themis Bio	P2		▪ *Potential candidate for EMA Article 58 given the target market*

1 Non-exhaustive; 2 FDA warnings for multiple violations (cGMP); barred from applying to the FDA till these issues are resolved; 2 Both companies are developing the vaccine

B Implications for 'Article 58' from innovative medicinal products targeted at LMICs only





Implications for 'Article 58'

'Article 58' is applicable in certain innovative medicinal products and vaccines that target LMICs exclusively, including:

i. **Medicinal products and vaccines that do not qualify for FDA tropical review voucher (e.g., Chagas, Dapivirine Ring etc.)**

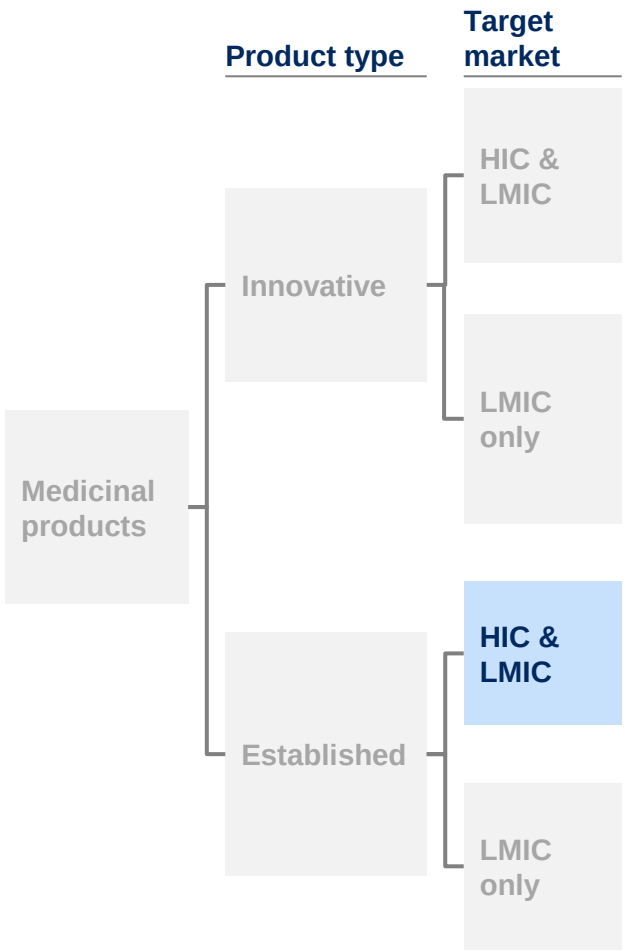
ii. **Medicinal products and vaccines where the risk-benefit perspective significantly differs between LMICs and HICs due to**:

- Differing prevalence and epidemiology of the disease (e.g., RotaShield, Sanofi ChimeriVAX)
- Differing standard of care/ medical practices (e.g., driving a high regulatory bar for clinical evidence for use in HICs)

iii. Products by **European manufacturers targeting LMICs exclusively who need a CPP (without marketing authorization in any EU country)**[1]

1 In some rare cases, manufacturers might obtain a manufacturing license (without marketing authorization) directly from their home European national regulator, allowing them to go to PQ and in LMICs without being subject to the sunset clause

C Implications for ‘Article 58’ from established medicinal products targeted at HICs and LMICs

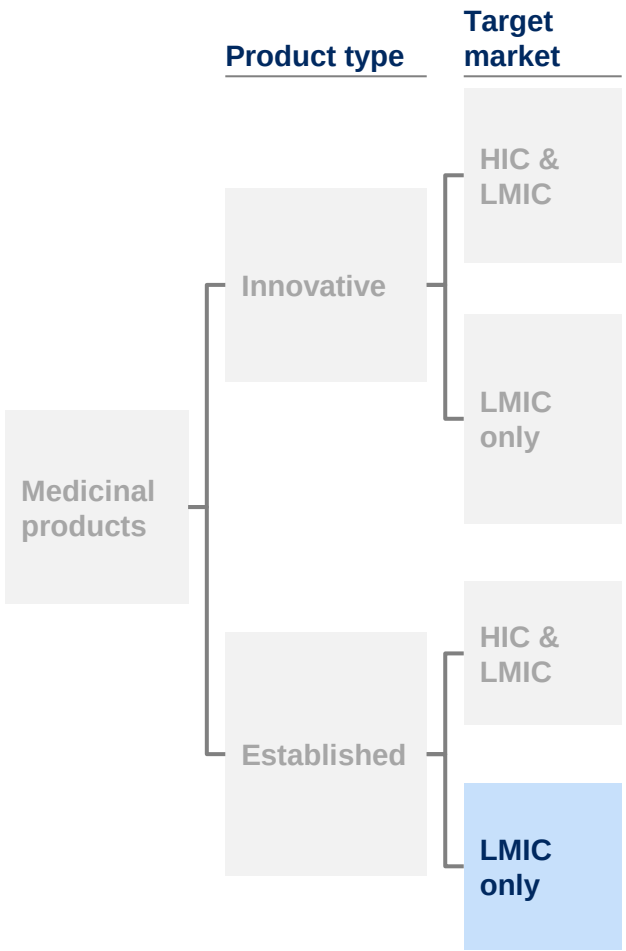


Implications for ‘Article 58’

Established products for HICs and LMICs are not suited to ‘Article 58’ in its current form

- The desire for marketing approval in HICs means that a manufacturer will choose the FDA central or EMA central pathways, as ‘Article 58’ prohibits European sales
- In addition, where the disease is primarily targeted at LMICs, a generics manufacturer will often chose a parallel pathway (i.e. going to PQ or directly to the LMIC’s NRA using the manufacturer’s home country approval)

D Implications for ‘Article 58’ from established medicinal products targeted at LMICs



Implications for ‘Article 58’

‘Article 58’ is well suited to serve certain established LMIC-targeted products

- ‘Article 58’ could serve as a primary pathway for established products that are targeted solely at LMICs where:
  - (iv) A manufacturer is creating a chemically and clinically identical, but physically distinct, product to combat re-importation risks (and wishes to gain a CPP through a body other than the WHO)
  - (v) A vaccine manufacturer based in a non-functional NRA, and so cannot go to PQ without first receiving an SRA approval
- Note that both these cases are relatively niche and may apply to a small number of products/manufacturers – though importantly there are only a few other regulatory pathway options for these manufacturers
- For most other generic medicines, manufacturers will chose to go directly to PQ or directly to the LMIC’s NRA using their home country CPP and marketing authorization

Against this landscape of regulatory pathways, Article 58 is primarily of interest to manufacturers of innovative, new products

Under review/ reviewed by Article 58

		Product type	Article 58 differen-tiated[1]?	Alternative pathways	Potential case examples	Comments	Relevance
Innovative, LMIC only	i	**Medicinal products and vaccines that do not qualify for the FDA priority review voucher**	✓	▪ FDA PEPFAR (ARVs only) ▪ FDA orphan ▪ Directly to target NRAs	• Fexinidazole (Sanofi)[3,4] • Dapivirine ring (IPM)	▪ FDA's TD PRV[2] is a powerful incentive and most manufacturers choose this pathway if their product is eligible ▪ 'Article 58' is an ideal pathway for cases where TD PRV is not applicable	
	ii	**Medicinal products / vaccines with significant variance in risk-benefit perspective between LMICs and HICs**	✓	▪ None	• ChimeriVAX (Sanofi) • RotaShield (Wyeth) • Ebola Vx (Merck, GSK) • **Hemoprostol (Linepharma)**	▪ Risk-benefit perspective driven by: – Country disease burden or epidemiology – Current standard of care or medical practices (driving reg. bar for clinical evidence)	
	iii	**Products by EU-based manufacturers that target LMICs exclusively and need an EMA CPP**	✓	▪ None	• Chikungunya Vx (Themis) • **RTS,S (GSK)**	▪ EU-based manufacturers require a CPP prior to LMIC registration[5] ▪ For some types of products[6], an EMA CPP is mandatory	
Established, LMIC only	iv	**LMIC-specific versions of medicinal products used to combat re-importation**	✓	▪ WHO PQ ▪ Tech transfer to Gx mfgr who in turn go to WHO PQ	• **Lamivudine (ViiV)** • **Aluvia (Abbvie)**	▪ Similar product is already approved by most SRAs / WHO ▪ Manufacturer cannot take product to them for extension of approval	
	v	**Vaccines produced by manufacturers based in countries with non-functional NRAs**	✓	▪ Directly to target NRAs	• Hepa-B (Incepta) • Ara-DTP (Arabio)	▪ Vaccines manufacturers based in countries with non-functional NRAs which currently cannot obtain WHO PQ	

1 Differentiation relative to other pathways; 2 Tropical Disease Priority Review Voucher (worth ~$200 m); 3 For Chagas and sleeping sickness; 4 will not qualify for FDA TDPRVs technical requirements; 5 The CPP could be from their home country or an SRA; 6 Eg. vaccines using recombinant DNA

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

Barrier	Description
Manufacturer/ stakeholder perceptions	▪ **Manufacturers unsure about the benefits** of the process for approval speed in LMICs ▪ Absence of successful example drives manufacturers' reluctance to use 'Article 58'
Cost of review process	▪ **High costs** (upfront and annual) prohibitive for small manufacturers ▪ Possibility and criteria for **fee waivers largely unknown** to manufacturers
NRA awareness and acceptance	▪ **Many NRAs still unaware** of 'Article 58' ▪ **Misperceptions** regarding the a potential "double standard" and the stringency of the review persist
Subsequent speed of NRA assessment	▪ For existing 'Article 58' approvals, **Article 58 has not translated to faster LMIC regulation** ▪ **Lacking formal mechanisms to share/leverage information** from 'Article 58' assessment and to expedite approvals
Closer integration with WHO PQ and collaborative registration	▪ 'Article 58' **drugs not part of WHO collaborative registration** ▪ **Abbreviated WHO PQ process for vaccines still takes up to 3 months** following a positive scientific opinion ▪ **Roles and responsibilities of WHO experts unclear** internally and externally

Contents

Over the coming years ~30 candidates are likely to consider 'Article 58'

Vaccine
Drug

	Disease targeted	Name of products (company)	Description / comment
Phase I	HIV/AIDS		▪ New formulation for PrEP[1] can increase adherence ▪ EU manufacturer, potential long acting formulation ▪ Useful against resistant HIV strains in LMICs
	Malaria		▪ Synthetic low-cost drug that matches WHO, MMV target profile
Phase II	Dengue		
	Lymphatic Filariasis		▪ Manufacturer that is looking for a route exclusively to Africa
	Malaria		▪ Potential to go through central pathway for prophylactic indications
	Schistosomiasis		▪ EU-based manufacturer for a disease that is primarily LMICs; regular routes will require the product to be marketed in EU
	TB		▪ EU-based manufacturer, recombinant vaccine for use in developing countries with require EMA approval
Phase III	Dengue		
	HIV/AIDS		▪ FDC with potentially lower side-effects in maintenance therapy, useful to reduce long term treatment costs in LMICs
	Leishmaniasis		▪ Focus of all three products is to build on Ambisome (today's best-in-class therapy) to treat this disease in LMICs
	Lymphatic Filariasis		▪ EU-based manufacturer for a disease that is primarily LMICs
	Malaria		▪ Prior experience with EMA may help fast-track this application ▪ Treats *P. vivax* – mostly prevalent in Indian sub-continent
	Measles		▪ Novel EU-based cell-line technology used for measles antigen, with which EMA is familiar India has low expertise
	Onchocerciasis		▪ EU-based manufacturer for a disease that is primarily LMICs
	Polio		
	Schistosomiasis		▪ EU-based manufacturer for a disease that is primarily LMICs

Overall strategic vision for ‘Article 58’

Strategic vision for an enhanced ‘Article 58’	**Increase LMIC access to high quality medicinal products by creating the fastest pathway to WHO PQ and LMIC review for highly impactful medicinal products**

	Today	Future
Overall	▪ Manufacturers **only use ‘Article 58’ if no other pathway available** ▪ Products reviewed to date had **limited registration success** in LMICs	▪ ‘**Article 58’ actively chosen** for its value in accelerating LMIC review ▪ **High-impact products** to go through ‘Article 58’
Benefits in terms of PQ and LMIC review speed	▪ WHO involvement guarantees **automatic PQ listing for drugs and abbreviated review for vaccines** within 90 days (but no access to WHO collaborative registration so far) ▪ **No acceleration** of LMIC review	▪ ‘Article 58’ to offer **clear speed advantages over other pathways,** incl. – Almost **instant WHO PQ approval** (for vaccines and drugs) after positive opinion – **Faster, priority NRA review** (through collaborative registration)
Additional manufacturer incentives	▪ **Potential fee waivers/reductions**, but criteria and extent of waivers unclear to manufacturers	▪ ‘**Article 58’ to offer clear incentives** to manufacturers
Communication	▪ **NRA awareness of ‘Article 58’ still mixed** ▪ **Some manufacturer misperceptions** persist ▪ **Few partnerships** with important stakeholders ▪ Messages not aligned with WHO	▪ ‘**Article 58’ well known and understood** by all stakeholders ▪ **Joint communication with WHO** and most important stakeholders

There are 5 enhancements to ‘Article 58’ that would help bring the strategic vision to life

Enhance value proposition

Create additional incentives to enable a less expensive and more widely recognised procedure through policy changes

Ensure faster WHO PQ process and/or access to collaborative registration post scientific opinion through better collaboration with WHO PQ

Further accelerate LMIC country review through capacity building and more consistent involvement of **NRAs as well as regional regulatory networks** in the ‘Article 58’ review process

Commu-nication

Clearly communicate the purpose, use and benefit of ‘Article 58’ through refreshed communication materials and develop a communications plan

Create partnerships with core stakeholders (e.g. donors, procurers and the WHO) to further embed ‘Article 58’ into the Global Health ecosystem

Article 58' playbook overview

1 Policy changes

- **Meeting between EC and EMA** to agree and then implement:
  - **Applicability of orphan designation and incentives** (such as fees reductions for protocol assistance) to eligible candidates choosing 'Article 58'
  - **Possible fee waivers** for the 'Article 58' procedure (to be clarified and communicated clearly to manufacturers)
  - Clarification that 'Article 58' does not exclude following a central pathway at a later stage (e.g. Hexaxim)
  - Possibility to run **'Article 58' and EMA central process in parallel**
  - New manufacturer **requirement for post opinions to report all post-opinion country approvals**

2 Collaboration with WHO PQ

- **Establish working group with WHO PQ** to:
  - Improve day-to-day collaboration with WHO, and coordination on variations, renewals and label changes
  - Coordinate with other stakeholders to ensure consistency between Article 58, PQ & WHO treatment guidelines
  - Create a **joint expert/NRA contact list** and **include national disease program contacts**
  - Agree **contact points** between EMA, WHO PQ, WHO disease programs, and WHO capacity building
- **Accelerate PQ** for both vaccines and drugs and enable **access to collaborative registration**
- Explore **back-to-back meeting** of CHMP/PQ/NRAs in London, immediately after positive 'Article 58' opinion
- Ensure product with next positive opinion obtains quick PQ and review by NRAs so it can be a **"poster child"**

3 Capacity building

- **Accelerate NRA review speed by increasing NRAs involved as observers, incl.**
  - Define new observer/expert logistics timeline to improve management
  - Explore potential increase of BMGF funding to facilitate increased NRA participation
  - Design more explanatory sessions/coaching during review attendance
- Align closely with important regional regulatory networks (e.g., provide "SRA" expertise for review of novel products)
- **Open existing EMA web training** to NRAs

4 Comms strategy

- Explore **rebranding** if changes to 'Article 58' are significant enough to justify costs
- Craft **new messaging, value prop** and info materials (differentiated for NRA and manufacturers)
- Create communication around **"poster child"** and fee waiver options

See compendium material

5 Stakeholder engagement

Manufacturers and PDPs

- **Reach out** to priority manufacturers **individually**
- Promote 'Article 58' at **select conferences**
- **Promote 'Article 58' earlier** through existing EMA meetings

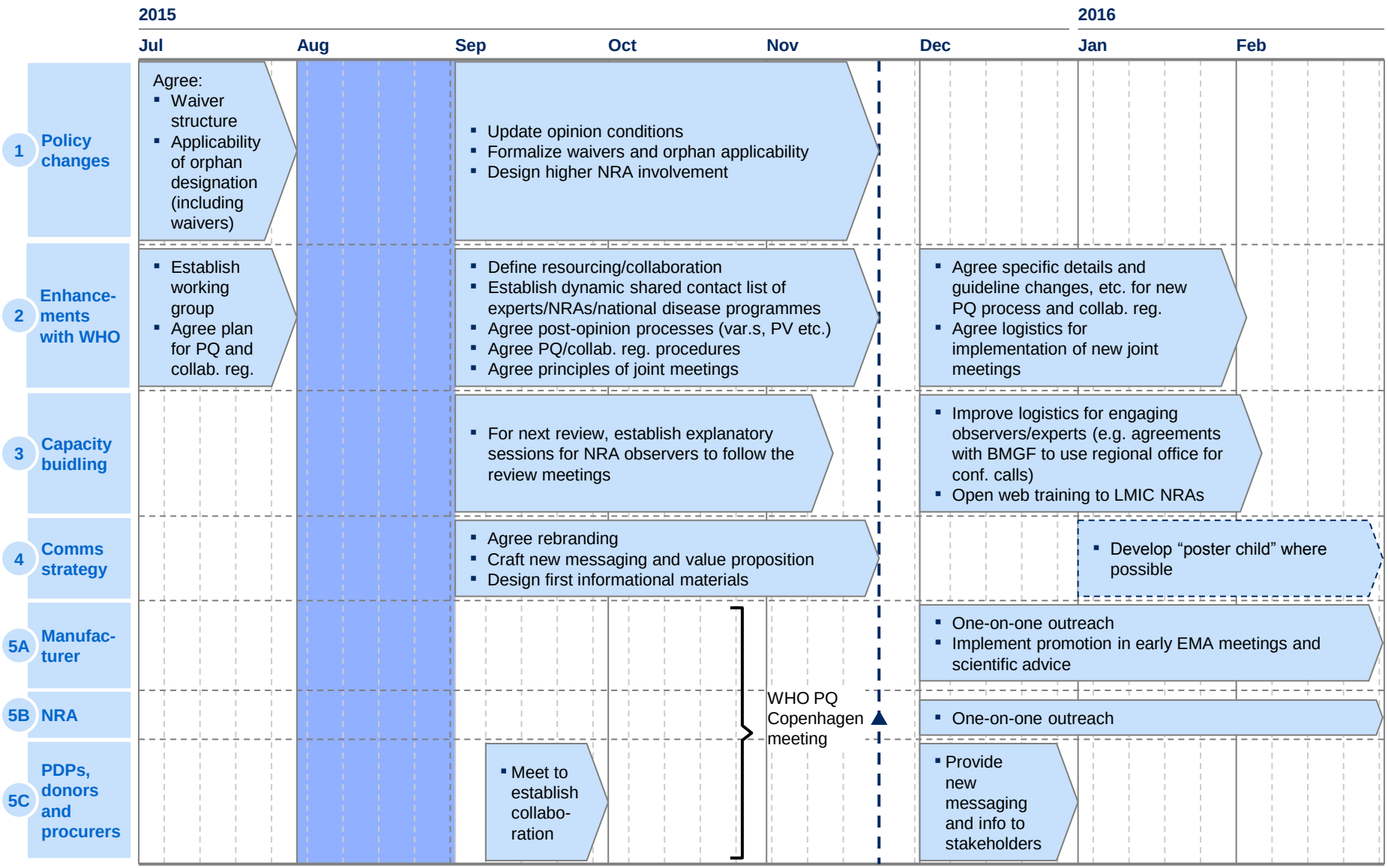
NRAs

- **Reach out** to priority NRAs **individually**
- Promote 'Article 58' at **select conferences**

Donors and procurers

- **Establish procurer relationships** to get 'end user' feedback and shape product priorities
- **Collaborate with procurers/donors** to address NRAs/manufacturers at their events
- **Explore funding** of application fees and observer attendance

Proposed high-level implementation plan for first 8 months



1 Three policy changes would make the 'Article 58' more attractive to manufacturers and help the post-approval monitoring

Target		Current situation	Options to explore
Strengthen incentives and benefits	**Apply orphan benefits by analogy**	▪ Several tangible incentives for EU central pathway with orphan designation, incl.: – Early designation as orphan – 10 years of market exclusivity in the EU – SME incentives (fee reductions of up to 100%, administrative and procedural assistance) – Access to research grants (through other EU programs)	▪ Allow a product that has orphan designation to still chose 'Article 58' as a possible pathway with the same incentives, incl. – Fee reductions – Access to research grants – Access to WHO funding ▪ Application of orphan benefits by analogy at discretion of EMA
	Fee waiver guidance	▪ Criteria of fee reductions not formalized and need to be granted case-by-case by Director General	▪ In case orphan benefits cannot be applied, set out clear reduction criteria (or examples) and ranges on the website (e.g. for SMEs)
Further enhance the post-approval monitoring	**Introduce new 'Article 58' reporting requirements**	▪ No visibility for EMA which national approvals are subsequently obtained by 'Article 58' products ▪ No opportunity for post-approval communication with NRAs on – Safety concerns – Drug variations – Label updates	▪ Make it a condition of a positive opinion that a manufacturer will report all national approvals (incl. variations) to EMA

Next steps

- **July:** Internal European Commission and EMA meeting to discuss which of these options could be explored over the coming months, and how they could be explored
- **September – November:** Carry out and formalise agreed changes
- **November onwards**: actively communicate these changes in chosen regulatory forums, etc.

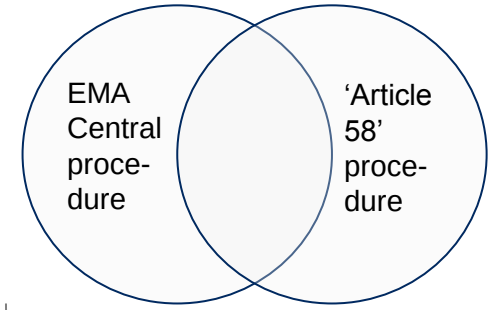
1 In the longer term, EMA could explore the option of a combined 'Article 58' and central pathway procedures

Current situation

- Most manufacturers want to obtain a EU marketing authorization – even if main market lies in LMICs
- 'Article 58' benefits ***(assuming 'Article 58' is enhanced)*** are not accessible to those manufacturers, incl.:
  - Faster PQ
  - Higher NRA involvement, both during scientific advice to shape clinical development as well as Article 58
  - Accelerated LMIC reviews

Option to explore

- Better communicate Hexaxim case example to illustrate how Central approval can be obtained after 'Article 58'
- Consider developing a pathway whereby manufacturer could benefit from both 'Article 58' advantages and EU Central pathway advantages (e.g. EU marketing approval, potentially fee waivers) while minimizing duplication of work or fees. Possible ideas/structure for pathway:
  - **During scientific advice**:
    - Manufacturer indicates both LMIC and EU target markets
    - EMA helps shape necessary studies required for review
    - Possibility for orphan designation remains
  - **Combined pathway involves**:
    - **Human resources**: Single rapporteur team, LMIC disease experts, NRA observers, WHO PQ and disease programs
    - **Timeline**: No increase to 210 day timeline
    - **Fees:** Single, central pathway fee structure (or slightly increased)



For combined pathway
- Additional content could be covered through a bridging study
- Need to explore feasibility of having two different benefit-risk analyses (for EU and LMIC) for identical product

2 A working group with the WHO should meet regularly to resolve challenges and further improve the collaboration on 'Article 58'

Detailed in following 2 pages

Suggested working group composition

- Involve senior officials on both the EMA and the WHO PQ side for a working group
  - **EMA**: *[Name redacted]*, 'Article 58' lead
  - **WHO PQ:** *[Names redacted] (at least for first meeting)*
- Work to be overseen by steering group (*[Names redacted]*)

Meeting frequency and form

- **Frequency:** Monthly
- **Location: in person in either Geneva or London**
- **Start date:** First meeting to be organized for July 2015
- **End date:** Meetings to be continued until challenges resolved or clear approach to resolve challenge established (latest in November 2015)

Objectives/ challenges to be resolved

- **Faster PQ review** for vaccines and drugs reviewed through 'Article 58'
- All 'Article 58' reviewed products to **access the collaborative registration**
- Newly installed **back-to-back meeting** of CHMP and PQ with NRAs in London, to take place the day after positive scientific opinion issued
- Smoother day-to-day collaboration through clear contact points/WHO coordinator and common contact pool
- Processes put in place for post-opinion **variations, label changes, renewals (e.g., GMP) and pharmacovigilance**
- **Coordination of positive opinion, PQ and WHO treatment guidelines**

- Working group should be created and meet for the first time in July 2015 to conclude the most important enhancements by late November in time for Copenhagen meeting
- If first meeting takes place after summer, the enhancements will likely not conclude before end of year

2 WHO PQ post an ‘Article 58’ positive opinion should be accelerated further and grant access to WHO collaborative registration

	Improve post-’Article 58’ PQ review speed	Ensure access to collaborative registration
Vaccines	▪ Allow submission of PQ dossier/information during ‘Article 58’ process to **enable parallel review of** – **‘Article 58’** – **PQ** – **Specific programmatic donor requirements**	▪ **Confirm ‘Article 58’ reviewed vaccines will be able to access collaborative registration** once collaborative registration for vaccines is launched
Drugs	▪ Allow accelerated WHO PQ review of ‘Article 58’ drugs, similar to centrally reviewed products ▪ Enable this review to start during ‘Article 58’ process, like for vaccines	▪ Officially include ‘Article 58’ reviewed drugs to collaborative registration

For greater efficiency and speed, WHO PQ meeting following the positive scientific opinion to happen back-to-back with final CHMP meeting in London to include the same EMA, NRA and WHO PQ participants

2 WHO PQ and EMA collaboration could be further smoothened out by nominating a WHO coordinator and by sharing NRA contacts

Nominate a coordinator / unique contact point on WHO side

- On WHO side, **nominate a coordinator** to
  - Liaise with EMA throughout the procedure
  - Represent a unique contact point for 'Article 58' for EMA, NRAs and other stakeholders
  - Coordinate WHO PQ and WHO programme involvement
- **Coordinator should be part of WHO PQ programme** and dedicate portion of time to 'Article 58'

Pool NRA contacts

- Together with NRA, **establish a dynamic list of existing experts, NRA observers and national disease program experts**, detailing
  - Contact details, organization and role
  - Previous 'Article 58' exposure
  - Area of expertise (disease area, geography)
  - Potential conflicted topics
- **Upload this information on a common platform** (shared drive or similar)
- **Align on who the WHO should best reach out to**
- **Update contact** list with latest / changed contacts, record latest interaction

Next steps (for all proposed WHO enhancements)

- **July 2015:** establish working group and in first meeting, agree on objectives for coming months
- **September – November:** Carry out and formalise agreed changes
- **November onwards**: jointly communicate these changes in chosen regulatory forums, etc.

3 To accelerate NRA approvals and build local capacity, more NRAs should have greater involvement in the review process

Target:
Every scientific opinion or scientific advice procedure should include at least 3 (ideally 5) NRA observers. Experts should provide insights to in-country clinical, epidemiology and pharmacovigilance aspects.

	Challenge	Potential solutions	Timeline
Identification of NRA experts and observers	▪ Identification and recommendation of NRAs too slow (part. for sci. advice) ▪ Too few NRAs involved in review; to date only: South Africa, Thailand, Ghana, Tanzania and Brazil for the 7 assessed products ▪ No national disease program participants included in process	▪ Establish shared contact lists of NRAs and experts *(see previous section)* ▪ Agree inclusion of national disease program experts in Article 58 review process where necessary	▪ Sept – Nov 2015 (together with WHO)
Financial	▪ High cost of hosting NRAs in London (flights, transport, hotel)	▪ Estimate cost of targeted NRA involvement and review BMGF grant to WHO PQ for NRA participation	▪ Sept 2015
Visa	▪ Last minute notification of NRAs ▪ Delays in visa applications preventing NRAs from participating	▪ Identify NRAs earlier and prepare visa applications ▪ Negotiate fast tracking or diplomatic visas with UK embassy	▪ To be implemented at next review
Other logistics	▪ Poor phone line connections ▪ Materials for CHMP meeting not shared or shared shortly before meeting ▪ Materials required in translation ▪ Erratic email communication that often relies on public providers such as gmail or yahoo	▪ Increase number of in-person meetings, including capacity building meetings to encourage broader NRA involvement ▪ Coordinate with BMGF and other donors to use local office facilities for critical NRA meetings and VCs	▪ To be implemented at next review
NRA coaching and preparation	▪ In past, roles and responsibilities of observers has been sometimes poorly defined/unclear	▪ Similar to recent initiatives for Mosquirix, ensure to – Clearly define observer involvement and expectations for involvement – Build specific capacity building/explanation sessions into review program	▪ Sept – Nov 2015 (together with WHO)

3 Cost estimation to involve 3–5 NRA observers per review process

Revised assumptions

	Initial assumptions				Revised assumptions			
	2015	**2016**	**2017**	**Total**	**2015**	**2016**	**2017**	**Total**
Total people per dossier	9	9	9		7[1]	7[1]	7[1]	
Number of trips p.p. / p.a.	2	2	2		2	2	2	
Total no of trips per year	18	18	18		14	14	14	
Airfare p.p. *(USD)*	2,000	2,040	2,081		2,000	2,040	2,081	
Total airfare expenses *(USD)*	**36,000**	**36,720**	**37,454**	**110,174**	**28,000**	**28,560**	**29,131**	**85,691**
Per day expense *(USD)*	470	479	489		470	479	489	
Duration per trip *(days)*	3.7	3.7	3.7		3.7	3.7	3.7	
Total per diem expenses *(USD)*	**31,302**	**31,928**	**32,567**	**95,797**	**24,346**	**24,833**	**25,330**	**74,508**
Total per dossier	**67,302**	**68,648**	**70,021**	**205,971**	**52,346**	**53,393**	**54,461**	**160,200**
No of dossiers p.a.	1	1	1		2	2	2	
Total	**67,302**	**68,648**	**70,021**	**205,971**	**104,692**	**106,786**	**108,922**	**320,399**

- Initiate discussions with donors to secure an additional ~ USD120k to be able to support NRA observer and expert participation in case applications increase to 2 / year

1 Including 4 NRA observers and 3 experts

3 Article 58 should also make efforts to align closely with regional regulatory networks on

	Pathway description	Participants
EAC Medicines Registration Harmonization project	▪ Launched in March 2012, with objectives of: – Developing harmonized documentation package – Building evaluator capacity – Streamlining management systems and processes – Developing systems to share regulatory information – Conducting joint dossier assessments and manufacturing site inspections	Burundi, Tanzania, Kenya, Uganda, Rwanda, WHO support
ZaZiBoNa	▪ Launched 2013, supported by SARPAM (S. African Reg. Programme on Access to Medicines and Diagnostics) and WHO ▪ So far, over 30 products have been assessed and 2 products (anastrozole and oseltamivir) have been finalised and recommended	Botswana, Zambia, Namibia, Zimbabwe
WAHO	▪ West African Medicines Regulatory Harmonisation Project launched by WAHO (supported by NEPAD) in early 2015	*15 member countries*
WHO joint assessment	▪ Ad hoc pilots with EAC countries in 2010 for marketing approval: – **Abacavir**: review/PQ/NRA approval in 7-12 months – **Amikacin**: review/PQ/NRA approval in 15 months	Various African NRAs, WHO
AVAREF joint assessment for clinical trials	▪ Recent ad hoc pilot to approve clinical trials of GSK's **Ebola vaccine**: – NRAs of Cameroon, Ghana, Mali, and Nigeria involved, with support from Health Canada, EMA, Swissmedic, and FDA – All participating NRAs have confirmed that they will respond to sponsor within two weeks	WHO, EMA, Various African NRAs, Swissmedic, FDA, Health Canada
Other	▪ NEPAD supports RECs' and countries' harmonization efforts through African Medicines Regulatory Harmonization Programme ▪ ASEAN regional harmonization initiative is emerging	NEPAD, ASEAN

4 A rebranding effort of ‘Article 58’ could be effective if the changes to ‘Article 58’ were substantial

Advantages of rebrand

- Opportunity for **‘fresh start’** to break with currently net-negative image of ‘Article 58’
- Possibility to **focus communication of** enhanced ‘Article 58’ around rebranding effort
- Chance to **design a catchier way to engage stakeholders not aware** of ‘Article 58’

Challenges related to rebrand

- **Cost and resources required** to
  - Develop new name and slogan
  - Adjust communication material
  - Update website
- **Potential confusion** caused among stakeholders familiar with ‘Article 58’
- Effort required to **align communication and messages with other stakeholders**

If the proposed enhancements to ‘Article 58’ are put into place, a rebranding effort would be beneficial

5 Proposed manufacturer/PDP and NRA engagement plan

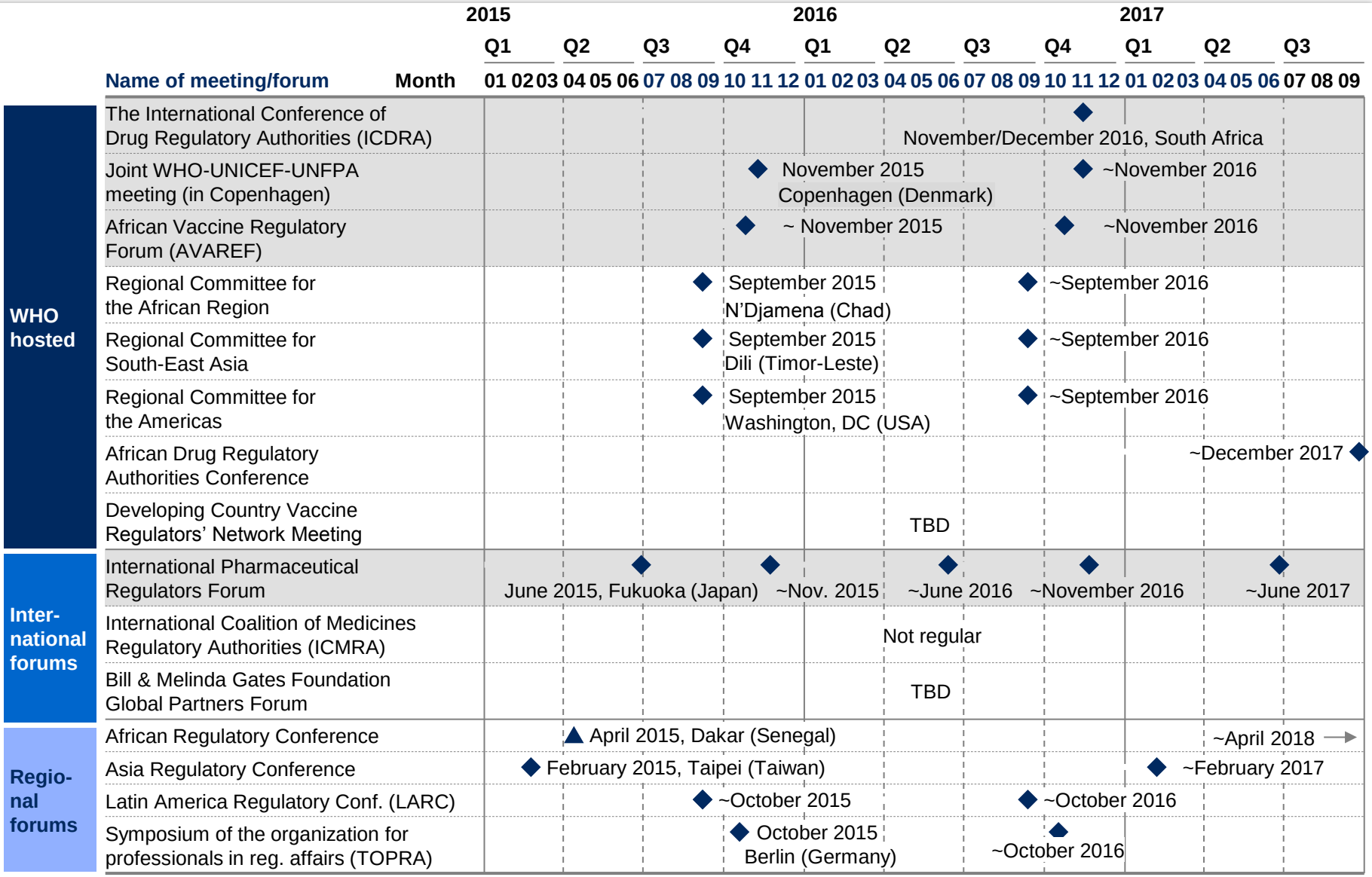
	Type of engagement	Example targets
Manufac-turers and PDPs	▪ **1-on-1 outreach:** directly reach out to most relevant manufacturers (based on pipeline analysis)	▪ ▪ ▪ *Names of sponsor companies have been redacted as commercial confidential information*
	▪ **Attendance of select conferences**	▪ DIA/IFPMA regulatory conferences ▪ GHRT (PATH) ▪ EFPIA[1] ▪ ICTRA
	▪ **Early EMA meeting promotion:** brief EMA colleagues to make manufacturers aware of 'Article 58' in early meetings	▪ Scientific advice meetings ▪ Innovation task force ▪ Pipeline project meetings
NRAs	▪ **1-on-1 outreach:** directly reach out to NRAs / regional harmonization groups	▪ E.g. DRC, Ethiopia, India, Nigeria, etc ▪ E.g. EAC, NEPAD, WAHO, ZaZiBoNa, etc
	▪ **Attendance of select conferences**	▪ The International Conference of Drug Regulatory Authorities (ICDRA) ▪ Joint WHO-UNICEF-UNFPA meeting (in Copenhagen) ▪ African Vaccine Regulatory Forum (AVAREF) ▪ International Pharmaceutical Regulators Forum

More information, and full list of conferences available in the compendium

1 EFPIA Annual Meetings attended by DG SANTE

5 Broader NRA advocacy should be conducted at appropriate conferences/forums, some suggestions:

Top priority



5 Donor/procurer engagement

Actions

- **Plan a trip to Geneva** (in September 2015) to meet:
  - **Global Fund**
  - **GAVI**
- Meet with other relevant stakeholders that could serve as thought-partners/ambassadors, e.g.:
  - IAVI
  - DNDi
  - MMV
  - PATH

Goals of engagement

- **Leverage donor/procurer events** (with manufacturers and/or NRAs) at which EMA could promote 'Article 58'
- **Present new 'Article 58' messaging**
- **Recruit donors/procurers as advocates** for 'Article 58' during manufacturer/NRA discussions
- **Identify opportunities for further collaboration**

Contents

The proposed enhancements outlined would create a stronger value proposition for applicants and differentiate ‘Article 58’

If the proposed short term enhancements are implemented, it would further enable Article 58 to

- Offer **rigorous scientific and manufacturing assessment**
- Allow **quicker prequalification** and NRA assessment timelines
- Create **attractive financial incentives**
- **Guarantee the involvement of WHO and local expertise** from scientific advice through to NRA assessment and into the post-authorization space

APPENDIX

SOURCE: Source

Medicines: several alternative pathways and incentives exist for LMIC-targeted products (1/2)

Advantage over other pathways
Neither advantage or disadvantage
Disadvantage

		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 procure-ment 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	• Accelerated variation approvals	• Fast-track WHO PQ approval • Automatic PQ listing	• Protocol/ marketing assistance • Fee reduction: Member state incentives • Fast-track WHO PQ	• Fast-track WHO PQ approval • Automatic PQ listing	• Fast-track WHO PQ • Tax credit[10] • Priority review voucher (last sold for ~USD 260m)	▪ Fast-track WHO PQ approval	▪ Fast-track WHO PQ approval	▪ 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

Vaccines: several alternative pathways and incentives exist for LMIC-targeted products (2/2)

Advantage over other pathways
Neither advantage or disadvantage
Disadvantage

Pathway benefits

	Pathways targeted at LMICs				Other SRA pathways (non-LMIC)		
	WHO PQ	EMA Article 58	EMA central	FDA TD PRV	Health Canada	Swissmedic	TGA
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 EU 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 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