

Artemisinin-based combination therapy in the treatment of uncomplicated malaria: review of recent regulatory experience at the European Medicines Agency

Eric Pelfrene^{a,*}, Marie-Hélène Pinheiro^b and Marco Cavaleri^a

^aOffice of Anti-infectives and Vaccines, Human Medicines Evaluation Division; ^bOffice of Regulatory Affairs, Human Medicines Research and Development Support Division; European Medicines Agency, 30 Churchill Place, Canary Wharf, London, E14 5EU, UK

*Corresponding author: Tel: +44 20 3660 8593; E-mail: eric.pelfrene@ema.europa.eu

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Malaria remains a major public health challenge with almost half of the world's population exposed to the risk of contracting the illness. Prompt, effective and well tolerated treatment remains one of the cornerstones in the disease management, with artemisinin-based combination therapy the recommended option for non-severe malaria in endemic areas with predominant *Plasmodium falciparum* infections.

Recent experience has been obtained at the European Medicines Agency with regulatory approval of two such antimalarial fixed combination products. For these cases, two different regulatory pathways were applied. As such, the present contribution describes this experience, emphasising main differences and applicability offered by these regulatory choices.

Keywords: Artemisinin, Article 58, European Medicines Agency, Malaria, Orphan drug, Prequalification of Medicines Programme

Introduction

Malaria is recognised as a major public health issue, affecting more than 90 countries with ongoing transmission and rendering nearly half of the world's population at risk. In 2012, an estimated 207 million cases occurred globally, causing around 627 000 deaths, mostly African children under five years of age.¹ *Plasmodium falciparum* and *P. vivax* account for most cases, with *P. falciparum* being the species causing substantial morbidity and the majority of the mortality.² *P. vivax* infection, although rarely life-threatening, nevertheless is responsible for important morbidity especially in young children that are the most vulnerable to severe outcome.^{3,4}

The multi-pronged strategy to fight malaria includes prompt diagnosis and treatment, reduction of the number of people being infected and control of the insect vector (indoor residual spraying, environmental management and biological control).⁵

With regard to the antimalarial treatment policy, the objective is to reduce morbidity and mortality by ensuring rapid complete cure of infection, in addition to curtailing the transmission of malaria by reducing the parasite reservoir of infection and infectivity. However, resistance is an increasing problem in the treatment of falciparum malaria, rendering conventional monotherapy less effective. Hence, to counter this threat and to improve treatment

outcome, WHO recommends that artemisinin-based combination therapy (ACT) be used for the treatment of malaria in areas where *P. falciparum* is the predominant infecting species. As such, pyronaridine tetraphosphate/artesunate (Pyramax) and piperazine tetraphosphate/dihydroartemisinin (Eurartesim), two newly approved ACTs, fulfil the WHO recommendation for the treatment of acute, uncomplicated malaria, providing a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of the partner component.¹ For both products, prequalification by WHO has been applied for and meanwhile already been obtained for one of them (Pyramax).⁶ This can be viewed as an important step as it provides option for bulk purchase for distribution in resource limited countries.⁷

The requested WHO prequalification, followed initial regulatory assessment and approval of both ACTs by the European Medicines Agency's (EMA, the Agency) main scientific committee (CHMP). For these products, the applications were submitted under different EU legal basis, as outlined in Box 1, i.e., Article 58 of EU Pharmaceutical legislation (No. 726/2004)⁸ in relation to Pyramax and EU Centralised Marketing Application route subsequent to the Orphan Designation⁹ of Eurartesim. Since the above EU regulatory pathways serve different main objectives, the article summarises this regulatory experience, describing strengths and limitations in

Box 1. Regulatory frameworkWHO prequalification⁷

Prequalification of new medicines is a WHO initiative, first established in 2001, to facilitate access to medicines that meet unified standards of quality, safety and efficacy and thus addressing an unmet need in countries with limited access to quality medicines. Although initially focused on HIV drugs, it has since expanded to encompass medicines for priority disease programmes.

Assessment of product data, by WHO staff and national regulatory authorities, is undertaken following voluntary submission of data by applicants, provided the medicines are on the WHO invitation list for 'Expression of Interest'.

Article 58⁸

Article 58 of Regulation (EC) No 726/2004 of the European Parliament and of the Council was established for the purpose of scientific opinion by CHMP in the context of cooperation with the WHO. The applicability is limited to prevent or treat diseases of major public interest, notably medicinal products for WHO target diseases (e.g., malaria, tuberculosis, HIV/AIDS, lymphatic filariasis, trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis, onchocerciasis, dengue fever, Chagas disease, leprosy and intestinal helminths), vaccines used or of possible use in the WHO Expanded Programme on Immunization (EPI), vaccines for protection against a WHO public health priority disease and vaccines that are part of a WHO managed stockpile for emergency response. It is meant exclusively for markets outside the EEA, but does not preclude a subsequent application for European Marketing Authorisation.

Orphan drug designation⁹

EU Centralised Marketing Application route forms the obligatory licensing pathway for a Community recognised Orphan Drug. The criteria of such designation as set out in Regulation (EC) No 1411/2000, require that the proposed medicinal product is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than five in ten thousand or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and no satisfactory method of diagnosis, prevention or treatment of the condition concerned is already authorised, or, if such a method exists, the medicinal product must be of significant benefit to those affected by the condition.

the use of these registration routes for new pharmaceuticals against tropical infections.

Regulatory evaluation of both ACTs

Pyramax film-coated tablets, fixed dose combination containing pyronaridine tetrakisphosphate and artesunate (P/A) (Shin Poong Pharmaceutical Co., Ltd, Korea), received a positive scientific opinion from CHMP in February 2012, for treatment of acute,

uncomplicated malaria infections caused by *P. falciparum* or *P. vivax* in adults and children weighing 20 kg and more.¹⁰ CHMP recommended a positive benefit-risk for use only as a single treatment course (once daily for three consecutive days) in any given patient and is limited to delineated geographic areas of low transmission with evidence of resistance to artemisinin containing therapy in line with the 'Global Plan for Artemisinin Resistance Containment Project' recently launched by WHO.¹¹

Following confirmation of eligibility by WHO, the application submitted in April 2010 in accordance with Article 58, had similar structure and content as applications intended for European marketing authorisations, but with caveat of being exempted from legally submitting any environmental risk assessment report or paediatric investigation plan (PIP). Nevertheless, paediatric subjects were adequately represented in the majority of these trials. Furthermore, at scientific opinion stage, the pharmaceutical sponsor committed to further develop an age appropriate dose formulation, suitable to the youngest (infants and children with a body weight ≥ 5 kg and < 20 kg). Since then, an application for supplemental approval of a fixed-dose granule formulation has indeed been received.

At the time of initial evaluation, two pivotal multicentre non-inferiority studies had been conducted in patients with uncomplicated *P. falciparum* malaria. These involved a total of 2543 adults and children weighing 20 kg and over and compared P/A with other artemisinin combinations (artesunate plus mefloquine [AS+MQ] or artemether/lumefantrine [A/L]).^{12,13} The main efficacy endpoint was PCR-corrected 'adequate clinical and parasitological response (ACPR)' at day 42, defined as the absence of parasitaemia, irrespective of body temperature, without the patient meeting any of the criteria of early treatment failure, late clinical failure or late parasitological failure according to WHO.¹⁴ As depicted in Table 1, non-inferiority was shown between treatments.¹⁵

Another study involved a total of 456 adults and children weighing 20 kg and over, suffering acute, uncomplicated *P. vivax* malaria.¹⁶ This non-inferiority trial, conducted at five sites in Asia, compared P/A with chloroquine standard treatment. In the efficacy evaluable population, 97.1% (202/208) of patients taking P/A were cleared of *P. vivax* parasites after 28 days compared with 97.0% (192/198) of patients treated with chloroquine (95% two sided CI for treatment difference = -3.5 to 3.9).¹⁵

Hepatotoxicity (increased liver transaminases) was the cardinal risk identified in these studies. Hence, the effect of repeat treatment courses of P/A needed first to be studied before possible introduction of this new ACT in high transmission settings, e.g., Equatorial Africa. An ad hoc expert group, which included independent advisors to WHO and an observer from an African regulatory authority, concluded though that in the meantime P/A could be an important gain to the therapeutic armamentarium in geographic areas of low transmission with recognised/rapidly emerging ACT resistance, involving resistance to the partner component (e.g., amodiaquine, lumefantrine, mefloquine and piperaquine). As such, its initial use has been restricted to a few areas within the Asia Pacific region. Cohort Event Monitoring for liver function is planned in the initial launch countries whilst focus is also placed on enhanced post-marketing surveillance in special populations (e.g., patients with HIV/AIDS, severely malnourished patients and pregnant women). A pregnancy register will be set up to monitor the outcomes of treated pregnant women in Africa, once the terms of use have been broadened

Table 1. PCR-corrected ACPR in EE population (Pyramax pivotal trials - *Plasmodium falciparum*)¹⁵

	Study SP-C-004-06		Study SP-C-005-06	
	Pyramax n=698	AS+MQ n=339	Pyramax n=746	A/L n=342
Patients excluded from the EE population PCR-corrected ACPR on Day 42	150 (17.9%)	84 (19.8%)	103 (12.1%)	81 (19.1%)
Available observations	698	339	746	342
Number of patients cured (cure rate)	661 (94.7%)	329 (97.1%)	729 (97.7%)	337 (98.5%)
Between group comparison				
Difference		-2.4		-0.8
95% CI ^a		-4.7 to 0.4		-2.4 to 1.3
Conclusion ^b		Non-inferiority		Non-inferiority
p-value ^c		0.088		0.374

ACPR: adequate clinical and parasitological response; AS+MQ: artesunate + mefloquine; A/L: artemether-lumefantrine; EE: efficacy evaluable (all randomized patients who received any amount of study treatment, excluding those with new infections and those lost to follow-up prior to analysis time point).

Study SP-C-004-06: A Phase III Comparative, Open-Label, Randomised, Multi-Centre, Clinical Study to Assess the Safety and Efficacy of Fixed Dose Formulation Oral Pyronaridine/Artesunate (180:60 mg Tablet) Versus Mefloquine (250 mg Tablet) Plus Artesunate (100 mg Tablet) in Children and Adult Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria.

Study SP-C-005-06: A Phase III Comparative, Double-Blind, Double-Dummy, Randomised, Multi-Centre, Clinical Study to Assess the Safety and Efficacy of Fixed Dose Formulation of Oral Pyronaridine/Artesunate Tablet (180:60 mg) Versus Coartem (artemether/lumefantrine) in Children and Adult Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria.

^a The two-sided CI for between group comparison was calculated using Newcombe-Wilson method.

^b Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -5%.

^c χ^2 test for superiority (performed only when non-inferiority had been demonstrated).

(based on further, recently submitted data) to make that region eligible for treatment.

In May 2012, three months following CHMP opinion, the WHO prequalification programme added Pyramax to its list of recommended medicines. Since then, based on WHO prequalification, National Regulatory Authorisations for Pyramax have been submitted in countries of the Greater Mekong subregion.

Eurartesim (piperazine tetraphosphate/dihydroartemisinin; PQ/DHA) film-coated tablets (Sigma-Tau Industrie Farmaceutiche Riunite s.p.a., Italy) received an EU Commission Decision in October 2011 (approving its use in the European Economic Area [EEA]), indicated for the treatment of uncomplicated *P. falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more. This followed a positive scientific opinion issued by CHMP in June 2011.¹⁷

PQ/DHA was designated as an orphan medicinal product during August 2007 for the indication 'treatment of malaria', based on assessment that the condition is rare (mainly to be viewed as 'import pathology' in returning travellers from endemic areas and migrants returning from visiting friends and relatives) though potentially life threatening to those affected and although other satisfactory treatment has been authorised in the EU Community, presumptive justifications were that the product may be of significant benefit to those affected by the condition.

The marketing application dossier contained an EMA Decision on the agreement of a PIP, with some measures deferred at time of submission of the marketing application (July 2009). As

per agreed PIP, a separate paediatric formulation will be submitted in future covering the vulnerable group of children, aged six months to five years.

The effects of PQ/DHA were first tested in experimental models before being studied in humans.¹⁸ Also, as part of the requirements, the applicant conducted an environmental risk assessment for both active substances.

This fixed dose ACT was further investigated in two main studies in patients with uncomplicated *P. falciparum* malaria.^{19,20} In the first trial, conducted in 1150 predominantly adult Asian patients, the aim was to demonstrate that the PCR-corrected cure rate of PQ/DHA was non-inferior to that of the comparator (AS+MQ). This cure rate was defined as the proportion of patients with ACPR at Day 63 plus those treatment failures identified as new *P. falciparum* (by PCR) and non-falciparum infections. Those patients lost-to-follow up for unknown reasons before Day 63, were excluded from intent-to-treat (ITT) population (m-ITT analysis). Non-inferiority was shown if the lower limit of the one-sided 97.5% CI for the difference between groups was greater than -5%.

In the second trial, PQ/DHA was compared with another anti-malarial ACT, containing A/L (tablets 20 mg/120 mg) in 1553 African children (minimum age of 6 months; mean age 2.4 years). The main measure of efficacy was the proportion of patients who were cured at day 28 of follow-up (PCR corrected results). Those patients lost-to-follow up for unknown reasons before day 28, were excluded from ITT population (m-ITT analysis). For both trials, non-inferiority outcome was derived (Table 2).

Table 2. PCR-corrected ACPR in m-ITT population (Eurartesim pivotal trials - *Plasmodium falciparum*)¹⁸

	Study DM040010		Study DM040011	
	Eurartesim n=726	AS+MQ n=361	Eurartesim n=1027	A/L n=497
Patients excluded from the m-ITT population	43 (5.6%)	20 (5.3%)	12 (1.2%)	17 (3.3%)
PCR-corrected ACPR				
Available observations	726 ^a	361 ^a	1027 ^b	497 ^b
Number of patients cured (cure rate)	704 (97.0%) ^a	344 (95.3%) ^a	952 (92.7%) ^b	471 (94.8%) ^b
Between group comparison				
Difference		1.7		-2.1
LL 97.5% CI ^c		-0.8		-4.6
Conclusion ^d		Non-inferiority		Non-inferiority
p-value ^e		0.161		0.128

ACPR: adequate clinical and parasitological response; AS+MQ: artesunate + mefloquine; A/L: artemether-lumefantrine; LL: lower limit; m-ITT: modified intent-to-treat (all randomized patients who received at least one dose of study treatment, excluding those lost to follow-up for unknown reasons).

Study DM040010: A Phase III, Randomised, Non-Inferiority Trial, to Assess the Efficacy and Safety of Dihydroartemisinin + Piperavaquine Phosphate (DHA/PQP, Artekin) in Comparison with Artesunate + Mefloquine (AS+MQ) in Patients Affected by Acute, Uncomplicated *Plasmodium falciparum* Malaria.

Study DM040011: A Phase III, Randomised, Non-Inferiority Trial, to Assess the Efficacy and Safety of Dihydroartemisinin + Piperavaquine Phosphate (DHA/PQP, Artekin) in Comparison with Artemether + Lumefantrine (A/L, Coartem) in Children with Uncomplicated *Plasmodium falciparum* Malaria.

^a PCR-corrected ACPR on day 63.

^b PCR-corrected ACPR on day 28.

^c The one-sided CI for between group comparison was calculated using the normal approximation (Wald method).

^d Non-inferiority was concluded if the lower limit of the one-sided 97.5% CI for the difference was above -5%.

^e χ^2 test for superiority (performed only when non-inferiority had been demonstrated).

Electrocardiographic QT interval prolongation (corrected for influence of heart rate; prolongation defined as QTcB or QTcF >450 msec in adult males and children up to 12 years of age or >470 msec in adult females), albeit asymptomatic in all cases observed during clinical trials, has been identified as principal safety concern. The QTc effect and associated clinical outcomes (torsade de pointes, sustained arrhythmias, sudden death) are flagged as important identified concerns in the risk management plan. During the marketing application process, an ad hoc expert committee gathered to discuss the cardiac safety aspects of PQ/DHA and concluded that the fixed dose ACT poses an unpredictable risk for a small proportion of people, but that based on pharmacokinetic considerations, cardiac risk could be further contained by administering PQ/DHA in fasting state.

Clinical data were missing from some patient populations, such as pregnant and lactating women, children younger than 6 months of age or below 5 kg body weight, elderly, HIV infected and malaria patients with Caucasian ethnicity. Regarding the latter, results from a pharmacokinetic study revealed there were no significant differences in exposure between healthy Caucasian and healthy Asian volunteers. Also, the effects in pregnant women exposed to PQ/DHA are to be monitored in a European multi-centre pregnancy registry, whilst PQ/DHA has also been included in the PREGACT project, which studies safety and effectiveness of various ACTs for African pregnant women with malaria.²¹

On obtaining the marketing authorisation, the orphan drug criteria were re-assessed, mainly to confirm the significant benefit over existing therapy. At that time, first line treatment for the condition in the EEA mainly offered choice between fixed combinations atovaquone/proguanil and artemether/lumefantrine oral treatment, with the latter being the only previously approved ACT for use in the European market.²² It was argued that PQ/DHA fasting dosing regimen may offer an advantage in clinical practice, since malaria patients are frequently nauseated. Further on, the sponsor considered that PQ/DHA could provide a valuable alternative treatment option for the returning traveller, even from regions with recognised artemisinin resistance (Cambodia and border regions of Thailand with Myanmar),²² since such resistance is considered fluid, largely influenced by the partner drug used in the ACT and thus patients will still recover, provided that they are treated with an ACT containing an effective partner drug.²³ However, prior to completion of this evaluation, the applicant requested to relinquish the orphan designation status for this new ACT.

By the end of October 2012, Eurartesim was marketed in eight EU countries. Outside the EU, it was first launched in Cambodia in September 2012, whilst Ghana became the first African country to approve Eurartesim during early 2013. Since then it has become available in other key African states taking part in the African research phase IV INESS programme, gathering data on safety and effectiveness of new ACTs.²⁴

A dossier was submitted to WHO in June 2012 to add Eurartesim to its list of recommended medicines in the WHO prequalification programme.

Discussion

Article 58

WHO prequalification guides procurement decisions of United Nations agencies and other authorities (e.g., allowing disbursement by the Global Fund to Fight AIDS, Tuberculosis and Malaria) primarily for medicines used in treating HIV/AIDS, malaria, tuberculosis and for reproductive health.⁷ As a general principle, the approval requirements for prequalification are aligned to those set by stringent medicines regulatory agencies. Indeed, if a product has been previously assessed and approved by such a regulatory authority, an abbreviated evaluation procedure helps speed medicines through the prequalification process. Moreover, it is noted that no further assessment is required if scientific opinion was obtained under Article 58 of EU Pharmaceutical Regulation (No 726/2004), as demonstrated by the experience with Pyramax, which received quasi instant prequalification approval following its assessment by CHMP. This is in line with agreed EMA and WHO alignment evaluation procedures facilitating early access of such medicines of high public health need and underscores the aim of the Article 58 process. So far however, the Agency's experience with Article 58 has received a mixed reception. Earlier approvals were mainly intended to prevent re-importation into Europe of already available products (e.g., antiretroviral lopinavir/ritonavir fixed combination). Recently though, more substantial regulatory experience was gained, in relation to a hexavalent childhood immunisation vaccine (Hexaxim, Sanofi Pasteur, Lyon, France), misoprostol indicated to reduce post-partum bleeding due to uterine atony, in situations where intravenous oxytocin is not available (Hemoprostol, Linepharma, Paris, France) and also for Pyramax. The Article 58 process encourages early regulatory interaction with WHO experts in order to fully elucidate the benefit-risk within the applicable epidemiological context. Feedback obtained to date, also identified a further need to engage representatives of national regulatory agencies drawn from countries of intended use, to build understanding and trust in the purpose of the Article 58 procedure. This also chimes with the recent review by Doua and Van Geertruyden²⁵ covering registration of medicines for low-income countries, stressing the need for participation of such local expertise.

Of note, during the Article 58 evaluation of Pyramax, close collaboration took place with independent experts advising WHO on malaria. This guided the CHMP to reach a fully informed opinion on the benefit-risk balance of the product, specifically to its intended use in populations residing in endemic areas. Mainly guided by the uncertainties in the safety profile, carefully weighed against the obtained clinical trial efficacy data and the need of further ACTs, the experts recommended its initial use to be limited to areas with low malaria transmission and with evidence of resistance to ACTs, and this in conjunction to the adherence of stringent risk minimisation measures.

In parallel to authorised products for EU Community use, Article 58 products are indeed subject to ongoing obligations, e.g., regular periodic safety update reports and risk management plan updates.²⁶ The feasibility in collecting reliable data might be

challenging though in some target endemic countries. Therefore, the effectiveness of routine pharmacovigilance (expedited reporting) and of enhanced pharmacovigilance activities (registry and close monitoring) in the recipient countries need to be sufficiently reassuring prior to receiving a scientific opinion from CHMP. Once available in endemic areas, and in light of possible emerging safety signals, CHMP also retains the option to amend the initial scientific opinion provided to WHO.

A drawback though concerning the Article 58 scheme is the lack of incentives offered to the pharmaceutical industry. Indeed, no automatic fee reductions or exemptions are in place although these can be granted on a discretionary basis, by Executive Decision.²⁶ At least this is perceived as cumbersome, since independent requests for such fee reduction have to be made at various stages of the product's life cycle, e.g., in relation to scientific advice, main application fee, different inspection fees and annual retention dues. Motivated reasons have to be provided in terms of public health need and minimal financial returns potential for the commercial sponsor relative to the substantial development costs.

Orphan drugs

In contrast to the above, the European pharmaceutical legislation offers multiple incentives within the framework of the orphan drug designation,⁹ as illustrated in Table 3. If granted orphan drug designation by the European Commission, regulatory scientific assistance (protocol assistance) may be offered partially or totally free of charge and various regulatory fees be waived in part or in total. In addition, on re-examining and reconfirming the orphan status at time of licensing, the product obtains marketing exclusivity in the EU for 10 years duration; i.e., 'the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a "similar" medicinal product'.⁹

Regarding Eurartesim, this new ACT easily fulfilled the first two criteria of the orphan drug designation by the fact that acute malaria has an annual disease incidence rate of around three new cases per hundred thousand population in the EEA²⁷ and that the condition can rapidly progress to a complicated course and be fatal, especially if left untreated in non-immune European patients.²⁸⁻³⁰ The innovator also argued significant benefit over existing therapy already authorised in the EU, based on administration advantage (fasting) and by offering an alternative treatment option to the returning traveller, even if returning from areas with recognised artemisinin resistance. Prior to completion of the re-assessment of the orphan drug criteria by the Agency's Orphan Committee though, the commercial sponsor of Eurartesim voluntarily chose to withdraw the orphan drug status, foregoing subsequent market exclusivity. In this context, it has previously been questioned if market exclusivity afforded to orphan medicinal products indicated for tropical infectious diseases indeed serves the best interest of the wider community, since arguably it may rather hinder the development of new medicines in the same therapeutic area.³¹ So far, this concern seems not yet borne out in practice. Conversely, experience shows that the orphan drug legislation had some catalysing effect, especially on smaller sized companies with new business models

Table 3. Article 58 versus Orphan Designation: comparison of requirements and incentives

Regulatory aspects	Article 58 Medicinal Product	Orphan Medicinal Product
Pre-submission phase		
Eligibility	Needed (in collaboration with WHO)	Needed (assessed by COMP)
SME status	Can be granted	Can be granted
Scientific advice	Possible	Possible
PIP	Not legally required	Legally required (compliance check prior to MAA submission)
Accelerated review request	Possible	Possible
Evaluation phase		
Environmental risk assessment	Not legally required	Legally required
Data applicable to EU population	Not required	Required
Application fee reduction	Eligible (case-by-case)	Yes ^a
Inspections fee reduction	Eligible (case-by-case)	Full fee reduction
CHMP opinion		
Conditional or exceptional circumstances	Possible	Possible
Post-opinion phase		
Marketing authorisation (EEA)	No (allows future MAA submission in the EU)	Yes
Market exclusivity	No (since no EU MAA)	Yes
PhV system / RMP	Needed (adapted to local use)	Needed
PSUR	Submission mandatory	Submission mandatory
Fee reductions	Eligible (case-by-case)	Yes ^a

COMP: Committee for Orphan Medicinal Products; EEA: European Economic Area; EMA: European Medicines Agency; MAA: marketing authorisation application; PhV: pharmacovigilance; PIP: paediatric investigation plan; PSUR: periodic safety update report; RMP: risk management plan; SME: micro, small and medium-sized enterprises.

^a See details in the explanatory fee note: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/04/WC500164415.pdf

(partnerships with non-profit organisations) and academic institutions in their quest to develop new medicines combatting tropical infectious diseases.³² It is also stressed that market authorisation would only be denied if there would be similarity in structure and mechanism of action to a previously licensed orphan medicine with the same therapeutic indication. In case of confirmed similarity, derogation rules exist based on obtained consent from the marketing authorisation holder of the earlier approved orphan product, supply shortages for that product already on the market or if the newer product is safer, more effective or otherwise proves to be clinically superior over the previously authorised orphan medicinal product.³³

With regards to EU licensing (either as orphan or non-orphan drug), it is however remarked that the benefit-risk balance derived on the use of a product directed against a tropical infectious pathology shows inherent relevance to the European population. Hence, it does not necessarily account for the local context encountered in low/middle-income countries (e.g., in relation to implementation of the safety specificities), although large study data gathering would normally only be feasible outside the EU Community, i.e., within endemic areas.

Specifically, in relation to studies on malaria treatment, adult and paediatric patients enrolled in regions, characterised by low, seasonal transmission (Australasia, Central and South America),

can act as a valuable proxy and thus be predictive for outcome in non-immune European travellers. This is though in contrast to the situation in sub-Saharan Africa, with its perennial and intense transmission dynamics, rendering most adults and older children (semi)-immune to clinical attacks. Therefore, non-immune children under five years of age are usually the segment of the African population most susceptible to symptomatic malaria.³⁴ They act as further proxy for EU patients with malaria and lend additional support to the paediatric extension of the therapeutic indication. Nevertheless, the pharmacokinetic profile may differ substantially between ethnic populations, largely due to genetic polymorphism.³⁵ Differences can either result in poor treatment outcome associated with sub-optimal drug exposure or observed increased toxicity based on overexposure.³⁶ Hence, bridging pharmacological data form a standard requirement in support of a European authorisation.³⁷ Such supplementary data were obtained for Eurartesim, comparing the pharmacokinetics of piperazine tetraphosphate and dihydroartemisinin between subjects grouped by ethnic origin (Caucasian versus Asian).

Also, the European marketing authorisation requires a paediatric plan to be submitted for assessment and opinion by the Agency's paediatric scientific committee, prior to submission of the main marketing application. The agreed PIP will set out the conditions and further tests to be undertaken in the paediatric

subpopulations, with often these measures initially deferred. Specifically, in aid of the youngest, a separate paediatric formulation might need to be developed.

Finally, notwithstanding the consideration by a given pharmaceutical innovator to bring the newly approved anti-infective agent to the market in a non-EU endemic area, using the EU authorisation as a valid basis (e.g. for subsequent prequalification process), the European licensing route puts the obligation to actually place the medicinal product on the EU Community market, within 3 years following its authorisation. Failure to do so, would lead for the marketing authorisation to be ceased within the EU.

Conclusions

Article 58 scientific opinion and orphan drug marketing application are two valuable tools facilitating authorisation of medicinal products indicated for treatment or prevention of infectious diseases, burdensome to endemic areas outside Europe. As such, they form basis for WHO prequalification, allowing subsequent purchase agreements for use in resource limited countries.

Both regulatory options provide their own set of real and perceived regulatory advantages and drawbacks. Hence, the ultimate choice of regulatory route taken by the innovator will need to be aligned with their overall strategic objectives.

So far, in reference to tropical infectious diseases, both procedures remain largely untested. As such, the present contribution aims to disseminate our experience to date and to invite further interest in these regulatory pathways.

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