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REVIEW

Regulatory and health technology assessment advice on postlicensing and postlaunch evidence generation is a foundation for lifecycle data collection for medicines

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The understanding of the benefit risk profile, and relative effectiveness of a new medicinal product, are initially established in a circumscribed patient population through clinical trials. There may be uncertainties associated with the new medicinal product that cannot be, or do not need to be resolved before launch. Postlicensing or postlaunch evidence generation (PLEG) is a term for evidence generated after the licensure or launch of a medicinal product to address these remaining uncertainties. PLEG is thus part of the continuum of evidence development for a medicinal product, complementing earlier evidence, facilitating further elucidation of a product's benefit/risk profile, value proposition, and/or exploring broader aspects of disease management and provision of healthcare. PLEG plays a role in regulatory decision making, not only in the European Union but also in other jurisdictions including the USA and Japan. PLEG is also relevant for downstream decision-making by health technology assessment bodies and payers. PLEG comprises studies of different designs, based on data collected in observational or experimental settings. Experience to date in the European Union has indicated a need for improvements in PLEG. Improvements in design and research efficiency of PLEG could be addressed through more systematic pursuance of Scientific Advice on PLEG with single or multiple decision makers. To date, limited information has been available on the rationale, process

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or timing for seeking PLEG advice from regulators or health technology assessment bodies. This article sets out to address these issues and to encourage further uptake of PLEG advice.

KEYWORDS

drug development, effectiveness, health economics, medicines regulation, safety

1 | INTRODUCTION

Following approval of a medicinal product (including vaccines) on the basis of a positive risk–benefit balance, European regulators often request postlicensing evidence generation (PLEG).[1–3] Health technology bodies also see a role for the generation of postlaunch evidence to address uncertainties complementary to those of clinical development. As well as those requesting PLEG, study sponsors, clinicians, and patients are also deemed relevant stakeholders. Below, we review the background to PLEG requests, the learnings from PLEG conducted to date, and why scientific advice from decision makers on PLEG designs is warranted in order to improve study designs. With the potential for requests for evidence from different regulators and/or health technology assessment (HTA) bodies (HTAb), interactions between different decision makers on the design of such studies, is explored.

Sponsors conducting PLEG, which in many cases will be the medicinal product developers, can seek scientific advice on PLEG proactively from European regulators and/or HTAb. Although comprehensive numbers of such advice requests are low, anecdotally the trend appears to be increasing.

Given the wide potential impact of PLEG on decision makers and medicines, it is important to consider from the outset the nature of the advice that could underpin PLEG, and disseminate any learnings. Furthermore, the ability of developers to integrate PLEG advice in development plans successfully depends on available regulatory and HTA frameworks. Such information is limited.[4] Furthermore, a prerequisite to successful interactions is that parties have a common understanding of the meaning of key concepts and terms in addition to the processes to be followed. Therefore, this paper aims to serve as a review of the emergence of PLEG in Europe as an evidentiary source for decision makers, as well as a discussion tool for medicines developers and other stakeholders, to further the understanding of PLEG advice, to define terminologies and to facilitate further proactive PLEG Scientific Advice discussions on individual development programmes.

Box 1 defines terms used in this paper. The term PLEG will be used to refer to either the postlicensing or postlaunch setting as there is much overlap even though the timing may differ; where differences are notable, these will be highlighted.

BOX 1 Terms used in this paper.

Scientific Advice: The procedure to seek feedback from regulators or HTAb across the life cycle of a medicinal product according to their respective remits on a prospective plan for evidence generation relevant to that medicinal product.

Parallel scientific advice/consultation: The procedure to seek simultaneous feedback from EU regulators (coordinated by the European Medicines Agency), with HTAs (coordinated by the EUnetHTA) on plans for the evidence intended to support submissions at marketing authorisation or reimbursement of new medicines, in order to generate optimal and robust evidence that satisfies the needs of both regulators and HTAb.

Multi-HTA scientific advice/early dialogue: the procedure to seek consolidated recommendations from multiple participating HTAb on plans for evidence generation intended to support future evaluation by HTAb.
Request: Evidence which is requested by regulators and/or HTAb; in this context this refers to the "uncertainty to be addressed by PLEG"; a developer's request for advice submitted to regulators and/or HTAb is termed an *advice submission*.
Questions: The research questions posed by regulators and/or HTAb, or also termed in this context the "uncertainty to be addressed by PLEG"; not to be confused with the questions posed in the advice submission by the developer.
PLEG: Evidence to be generated in the postlicensing or postlaunch setting to address the remaining uncertainties associated with a medicinal product within the licensed indication.
Postlicensing: From a regulatory perspective, postlicensing evidence generation refers to additional data postauthorisation, as is necessary from a public health perspective to complement the available data with supplementary data about the safety and, in certain cases, the efficacy or quality of authorised medicinal products.
Postlaunch: From an HTA perspective, designates additional evidence collected while the health technology is accessible to patients outside of a research setting. For pharma products, data can be collected prelicensing in the context of compassionate use but more frequently postlicensing.
PLEG scientific advice: Seeking input from regulators and/or HTAb on the studies to address the uncertainty.
Reassessment: HTAb may conduct reassessment in different contexts i.e. listing renewal, new submissions from Medicines Developers a, mandate from appraisal committee or ministry of health (class review or individual assessment). HTAb can also decide on their own to reassess a product based on identification of new evidence.
EU, European Union; EUnetHTA, European Network of Health Technology Assessment; PLEG, Post-Licensing or Post- Launch Evidence Generation.

2 | PLEG CHARACTERISTICS

2.1 | PLEG definition and scope

PLEG is an umbrella term for evidence generated after the launch or licensure of a medicinal product within the approved or intended indication(s), and populations that could benefit under those indications. It complements evidence generation already undertaken for licensure or HTA appraisal, addressing remaining uncertainties but also potentially covering wider questions of disease management and healthcare delivery. PLEG forms part of an evidence generation continuum on a background of a positive benefit–risk profile of a product. Evidence generation to support extending the approved indications and populations for a licensed medicine is out of scope of this paper as this pertains to new data to support a risk benefit akin to an initial indication. HTAb give advice outside the licensed indication only in the context of a complete development plan where there is an intention to ask for an extension of indication.

PLEG study designs can encompass a wide range of study designs; randomised or nonrandomised trials, interventional or noninterventional studies, and pragmatic or explanatory trials. Data can derive from trials or from a wide array of other sources (e.g. medico-administrative/claims records, health care records) or data-capture mechanisms (e.g. registries, from wearable devices or smartphone apps).

Data can be generated in the context of specific requests (i.e. postauthorisation safety studies [PASS] or postauthorisation safety efficacy studies [PAES], HTA body requests for reassessment, or in the context of conditional coverage, conditional reimbursement or market entry agreements) or under the initiative of the developers or academics. PLEG can be based on data primarily collected for the set purpose, or on data collected for other reasons. PLEG can also include data from temporary authorisation of use programmes or early access to medicines schemes—which are run by national regulatory bodies and which aim to give patients with life-threatening or seriously debilitating conditions early access to medicines.

2.2 | PLEG rationale

PLEG may be instigated by various stakeholders (regulators, HTAb, developers, academic, patient organisations) and the rationale may vary by the stakeholder concerned. These are further considered below.

From a **regulatory** perspective, postlicensing evidence supplements the authorisation dossier with additional information about the safety, effectiveness or quality of authorised medicinal products. PLEG is used to address those questions that should only or can only be answered after regulatory approval based on positive risk–benefit balance. Instigating PLEG is not a means to enable approval of medicinal products in the absence of sufficient evidence to determine the risk–benefit. There is a hierarchy of uncertainties depending on the potential impact also reflected in the regulatory processes, ranging from those with the greatest potential impact down to recommendations for those with less impact.

Uncertainties for which studies are *imposed* by regulators at licensure will be those that are important enough to potentially impact on the product information and product's clinical use. The study should provide information to either complement initial evidence or to verify whether the marketing authorisation should be maintained as granted, varied, suspended or revoked on the basis of new data resulting from the study.[1,5] The circumstances, and categories of PLEG when *imposed* by regulators are shown in Table 1, depending on whether

TABLE 1 Marketing authorisation (MA) types, circumstances and categories of postlicensing or postlaunch evidence generation (PLEG) for European Union regulators[6]

Marketing authorisation type	Full MA	Exceptional circumstances	Conditional MA
Imposed PLEG type	Annex IID	Specific obligations	Specific obligations
Circumstances			
	Additional evidence key to benefit risk leading to potential changes to product information	The applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.	All the following must be met: • the benefit–risk balance of the product must be positive; • the applicant will be able to provide comprehensive data; • unmet medical needs will be fulfilled; • the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.
	PAES delegated act: Investigate uncertainties stemming from surrogate endpoint, combinations, subpopulations, long-term efficacy, change in standard of care, new scientific factors, or real-life conditions	Includes category 2 PASS, PAES.	Aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases, including orphan medicines, or for products intended for use in emergency situations.
	PAES imposed in the case of ATMPs, Paediatric use of marketed products, or pharmacovigilance referrals	Annual re assessment is needed	Includes category 2 PASS, PAES.
	Category 1 imposed PASS	Subject to requirements for the applicant to introduce specific measures	Annual renewal needed
Required PLEG	Includes category 3 PASS		
	Additional pharmacovigilance activities in the risk-management plan		
Recommended PLEG	Important considerations in view of the potential future use of a medicinal product by the MA		

ATMP, advanced therapy medicinal product; PAES, postauthorisation efficacy studies; PASS, postauthorisation safety studies.

the product is licensed as a full, conditional or exceptional marketing authorisation (MA).

For uncertainties with potentially less of an impact on the product profile but which are still important, regulators can *require* studies by (e.g. category 3 PASS) or *recommend* further studies. These differences in regulatory categorisation are reflected in the consequential levels of obligations for handling of protocols and study results.[6,7]

Other regulatory jurisdictions, such as USA,[8–10] Canada[11] and Japan,[12–14] also have frameworks and criteria for postauthorisation commitments.

In the context of **HTA**,[1,15–17] postlaunch evidence can be requested for different purposes i.e. refining the relative clinical and economic value of a new product with relevant outcomes measures for patients, informing on a product's use in clinical practice (e.g. its place in the treatment algorithm, treatment duration, adherence), contributing to market access agreements, conditional financing mechanisms or conditional coverage defined by pricing and reimbursement decision makers. In this latter context, PLEG implementation could be the condition for medicine access. In any case, PLEG will be considered at reassessment by HTAb. To guide HTAb regarding PLEG requests during an initial HTA assessment, the European Union Network for Health Technology Assessment (EUnetHTA) has developed selection and prioritisation criteria for PLEG.[18] See Box 2. In considering whether PLEG is necessary, HTAb need to understand how uncertain a decision based on expected cost-effectiveness or population net health effects is and what the opportunity cost for other patients might be if an incorrect decision is made. In a paper by Claxton et al.[19] there is a suggested approach for determining whether further research is necessary or not and what further evidence would be needed. PLEG should answer those questions that cannot be answered at initial appraisal.

Stakeholders for vaccines, include, in addition to the regulators, **National Immunisation Technical Advisory Groups** (NITAGs), which

BOX 2 Selection/prioritisation criteria for European Network of HTA ADC at initial HTA assessment.[18]

Primary criteria: eligibility for ADC?

1. Did you identify any critical evidence gaps during HTA? *(yes, no)*
2. Is the research question explicitly defined? *(yes, no)*
3. Is ADC feasible (especially in terms of timeframe, type of study, population and costs)? *(yes, no)*
4. Is this study necessary taking into account similar planned/ongoing studies?

   a. *Yes*, because there is no similar planned/ongoing study elsewhere.
   b. *Yes*, because even though there is a similar planned/ongoing study elsewhere, there is an additional value of performing this 1 too.
   c. *No*, because the similar planned/ongoing study will bring sufficient information.

5. Will the additional data to be collected bring a significant added value for the subsequent HTA and decision making? *(yes, no)*

Secondary criteria: further selection and prioritisation

1. Burden of target disease (mortality, morbidity prevalence, incidence, disability-adjusted life years, quality-adjusted life years)
2. Expected benefit of the technology (on the burden of disease/on the management of disease/economic benefit/organisational/social benefit)
3. Potential of the technology to cover unmet health care needs or to substantially improve the health care compared to existing alternatives
4. Importance of ADC for confirming expected benefit and/or monitoring/optimising the conditions of use.
5. ADC, Additional Data collection; EUnetHTA, EuropeanNetwork of Health Technology Assessment; HTA, Health Technology Assessment.

are multidisciplinary expert groups providing advice to policy makers and programme managers on policy issues related to immunisation and vaccines. These operate at the national level. Public health authorities/NITAGs have also requested PLEG.

Lastly, the **developer** may wish to conduct additional voluntary studies to support further development of approved products in Europe as well as globally, or studies may be undertaken voluntarily by **academic** groups.

2.3 | What PLEG has been requested previously?

To further support the understanding of PLEG requirements, available information from regulators and HTAb on previous PLEG requests have been collated to provide insight into frequency, objectives, study designs, data sources, compliance and potential impact.

EU **regulators**[1]reviewed the compliance of marketing authorisation holders with their postauthorisation obligations for all EU medicines for human use authorised centrally between 2012 and 2016. Of 393 included medicines, 102 products (26%) had obligations across all licence types (full, conditional and exceptional MA), including all legal bases (new active substance, known active substance, fixed combination, informed consent, well established use and hybrid applications). Qualitative analysis from this study showed that for conditional MAs (CMAs), obligations typically related to submission of results from the phase II/III trials, which in many cases were ongoing at time of the European Medicines Agency (EMA)'s initial authorisation in order to confirm and further characterise the clinical benefits and risks. In the case of exceptional circumstances, further evidence on long-term real-life effectiveness and safety data, epidemiology of the disease, drug utilisation patterns, or quality of life data were requested.

Regarding impact, of those reaching their set milestone, 72% (36/50) provided additional information that was reflected in the product information. In the remaining 28% of cases, EMA considered that the results confirmed existing knowledge.

In the EU, in the interest of public health, applicants may be granted a CMA for medicines based on the criteria defined in legislation and guidelines e.g. medicines for human use may be in scope if they aim to treat, prevent or diagnose seriously debilitating, life-threatening diseases or orphan medicines, or to be used in emergency situations, and if all the necessary requirements are met: the benefit–risk balance of the product is positive, it is likely that the applicant will be able to provide comprehensive data, the unmet medical need will be fulfilled and the benefit to public health of immediate availability outweighs the risks due to need for further data. EMA reviewed 10 years of experience with this tool recently, including aspects relating to collection of additional evidence in this setting.[20] Notably, all conditionally authorised products had imposed obligations to collect additional data of between 1 and 4 activities. PLEG study designs here included randomised and nonrandomised studies; studies were both new and ongoing. Most imposed PLEG had an objective of clinical safety and/or efficacy. See Figure 1.

EU analyses of postauthorisation safety studies, and the use of registries are also available.[21–25] A review of EU centrally approved products between 2005–2013 indicated that EMA imposed PLEG through a *registry* in 4 and 29% of nonorphan and orphan medicinal products, respectively, and in 12 and 67% of products licensed under conditional or exceptional routes, respectively.[21] A review of EU products licensed centrally between 2007 and 2010 for imposed or required registries, indicated that the primary objective in 53% of 73 registries was safety data, while 10% also had assessment of real-world effectiveness as an objective.[24] Issues with registry-based studies included delayed start or completion of study, slow accrual, and

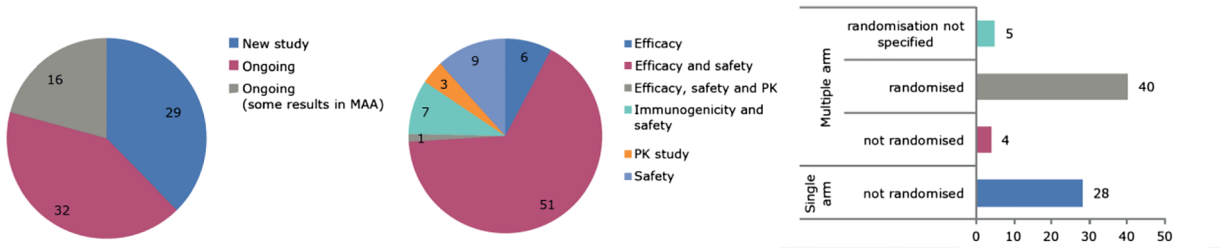

FIGURE 1 Status, objectives and design of studies imposed by regulators in conditional marketing authorisations from the report on 10 years of conditional marketing authorisation experience (n = 77).[20] MAA, marketing authorisation application; PK, pharmacokinetics

low data quality. These reviews confirm that well-designed studies based on disease registries may be more informative than studies based on single product registries. EMA has consulted on considerations for the use of disease registries for regulatory purposes.[26] Other nontrial sources beyond registries have been proposed in Scientific Advice for example using expanded access programmes and electronic healthcare records using novel designs (unpublished data, EMA).[27] A review of EU-funded initiatives for use of real-world data (RWD) explored the potential for these data in regulatory decision-making. This found that there are challenges for their utilisation based on limited data access, and lack of sustainability.[28] Equally, few European health care record databases met minimal regulatory requirements or were readily available to be used in regulatory decision making also owing to accessibility and validity issues.[29]

The challenges in conducting postauthorisation safety studies for vaccines include the requirement for valid exposure and outcome data (including brand-specific data), adequate data sources, and mitigating bias and confounding which, while not unique to vaccines, can be particularly complex in these settings. Vaccine developers highlight the need for assessing study feasibility, and interacting with public health authorities and regulators to confirm that study objectives can be met in a timely manner.[30] PLEG is commonly requested by regulators to further evaluate vaccine safety, and monitor real-world and long-term efficacy.

For more than 10 years, **HTAb** have used PLEG for assessment and appraisal purposes. In some countries (UK, France, Netherlands, Italy), PLEG contributes to access schemes put in place by pricing and reimbursement decision makers. Examples of practices among different HTAb are described in Table 2 together with the rationale, challenges and limitations of PLEG in these settings.

3 | ADVICE ON PLEG

3.1 | Why seek advice on PLEG

When a critical uncertainty that impacts on a product's potential benefit–risk profile and relative effectiveness has been identified, it is strongly recommended that the developer should seek advice as early as possible from the regulator/HTAb on how to generate PLEG to address the related research question. This recommendation is underpinned by the study challenges identified above in the reviews of PLEG carried out to date. Examples of advice on PLEG can be described where developers have come forwards with specific objectives for PLEG, and regulators have provided feedback on the prospective plan in a given setting; e.g. regulators accepting an open-label trial extension instead of a registry study, endorsing a pragmatic trial design, or explaining regulators' requirements for a post-CMA study. Table 3 below provides additional examples and uncertainties suitable for PLEG advice. The benefits of seeking advice are further explored below, and available information and guidance collated in terms of when and how to seek advice on PLEG.

3.1.1 | Increase quality, timelines and robustness of PLEG proposals

Critical review of PLEG proposals by regulators/HTAb with expertise in methodology and the disease area using the established framework for advice, will mean that the study question is addressed in the optimal way to the regulators' and HTAb requirements. This dialogue will facilitate understanding of the uncertainty and what is required by the decision maker to address it, complexities in particular settings, feasibility issues or other constraints.

It is important for all stakeholders that PLEG is undertaken in a timely way e.g. avoiding unnecessary delays to the start of safety studies once the medicinal product is launched on the market. PLEG implementation can have lengthy lead-in times e.g. adding additional modules in existing registries, data access issues, negotiation with health record/claims databases or registry owners, or designing primary data collection studies. An overly compressed time-frame for study planning may restrict potential study design and data source options. Where possible, having preparatory discussions through Scientific Advice before licensing means that PLEG study designs can be more advanced at the time of MA assessment or reimbursement appraisal than if proposals are put forward by developers or requested by regulators very late in the decision-making process.

3.1.2 | Use of RWD

Whilst there is some EU regulatory guidance on use of RWD for PLEG,[5,7,42–44] it may be necessary to seek advice so designs can be tailored to specific products and indications. Novel modalities integrating designs and data sources for example, in pragmatic trials or

TABLE 2 PLEG usage characteristics in European Union HTA bodies

HTA agency	Origin of the request	Data collected	Data source	Type and examples of products	PLEG usage	Challenges and limitations of PLEG
HAS (France)	The HAS transparency committee responsible for medicine appraisal formulate request to the company in the final assessment and appraisal document. Methodological guidelines as well as templates for protocol submission are available on HAS website[33,34]	Conditions of use, therapeutic value through effectiveness and safety outcomes	Increasing role for academic cohorts/registries and data from the French national insurance database	Medicines with current postregistration study requests[31,32]	Reassessment	Long discussions on protocol Delay to access data The quality of data
AIFA (Italy)	Data to be collected are defined (the dataset) by AIFA with the support of its technical scientific committee during the evaluation of the medicines for pricing and reimbursement purposes.	Data collected are related to demographic and baseline clinical characteristic of patients, follow-up data, end of treatment data, follow up after the end of treatment	Monitoring registries	Monitoring registries[35]	To reassess the product, to use data in the assessment of comparators (e.g. number of patients treated), to apply MEAs (both outcomes-based and financial-based), to guarantee the proper use of the medicines	Administrative and technical burdens
Spanish HTA	Implementation by HTA	Therapeutic value through effectiveness and safety outcomes	Pharmacoclinical data according to protocols and patient and treatment registration Five ad-hoc nonpharma registries started in the 2015–2019 period[38]	Advanced therapies and high-impact medicines for specific rare diseases such as hepatitis C direct-acting antiviral treatments, Nusinersen for the treatment of spinal muscular atrophy and CAR-T cells for the treatment of lymphoma and leukaemia.[36,37]	Monitoring data and evaluate the managed entry agreement stipulated between the marketing authorisation holder and the Spanish Ministry of Health. Support innovative contracting schemes in a regional HTA or hospital level such as risk sharing agreements since 2010[39] or the Catalan RPT 293 (Registre de Pacients i Tractaments) since 2012 Support the generation of additional data for financing decision making (nonpharma use)	The quality (completeness, quality …) of data can be a challenge. Experience in a national or generalised sense is still scarce.

TABLE 2 (Continued)

HTA agency	Origin of the request	Data collected	Data source	Type and examples of products	PLEG usage	Challenges and limitations of PLEG
RIZIV INAMI (Belgium)	Request to the company for clinical and volume data	Clinical data	New phase III studies the results of which were known later	Confidential information	Reassessments	Methodology
		Pharmacoeconomic data	Phase IV studies		Renegotiations of reimbursement	Completeness of some databases
			Claims database			Managed exit agreement
			Clinical registries			
ZIN (the Netherlands)		(Hard) clinical outcomes (e.g. survival quality of life)	Data from clinical practice, including registries, claims data, phase IV studies	Historically: orphan- and expensive drugs examples include drugs for Pompe and Fabry's disease, severe asthma (omalizumab) and breast cancer (Herceptin).	Either reassessments after a given period, or developing recommendations for appropriate use of drugs (e.g. start/stop criteria)	Scientific: biases in data collection and analyses, methodological challenges relating to population level effectiveness *vs* subgroup level effectiveness/ personalised health
		Economic outcomes (direct, indirect medical/nonmedical costs)		Now focus on orphan drugs and those licensed with conditional or exceptional licenses.		Policy: difficulties in taking hard measures (e.g. removal from insurance package) based on uncertain data.
				Usage example[17]		
NICE (England)	Collection of PLEG to inform managed access agreements (NHS England CtE scheme). CtE developed and refined with the NICE which advices NHS on the need, the selection criteria, outcomes and the length of follow-up measure, number of patient and centres, data sources.	Clinical effectiveness, cost-effectiveness, differential benefit between subgroup, impact of comorbidities	Data from registry	Many of the technologies approved through the cancer drug fund. Osimertinib.[40]	Once the CtE evaluation report is available, NHS England's published policy for the treatment concerned will be reviewed and a decision will be made with regard to whether NHS England will or will not make the treatment available within the NHS.	Data collection/governance, comparators, length of follow up, timing with primary data collection
G-BA (Germany)	G-BA request for registry data (including German patients depending on the indication) to be provided by the medicine's developer,	Clinical data that enable a comparison (direct or indirect) of relevant endpoints for efficacy and safety	Disease registries	Orphan drugs, ATMPs	Currently at the time of reassessment Registry studies/data are also evaluated during the initial appraisal if such	-Data quality (e.g. sufficient information on patient baseline characteristics, endpoint definitions, high amount of missing data) Comparative data for

(Continues)

TABLE 2 (Continued)

HTA agency	Origin of the request	Data collected	Data source	Type and examples of products	PLEG usage	Challenges and limitations of PLEG
	currently at the time of the initial appraisal of the product				data are submitted by the developer in the dossier	relevant patient population against standard of care- Limited experiences in the national setting with the usage of PLEG data
TLV (Sweden)	Implementation by TLV	National data from registries	The Swedish prescribed dispensed pharmacy registry	Haemophilia, NOAC, neuroscience, cardiovascular (PCSK9 and Entresto)	Reassessment or confirming previous assessments	Lack of efficacy variables and long timelines for merging different data sources of patient characteristics
FIMEA (Finland)	FIMEA's HTA reports include a chapter on PLEG. The aim is to identify the postlaunch evidence needs that would be the most valuable in reassessments.	FIMEA has no standard process for data collection and analyses in the context of PLEG. In the HTA reports, the identified PLEG needs typically include updated results from ongoing clinical trials and national RWD to describe the use and outcomes of the treatment (and its comparators) in clinical practice.	Data could be derived from number of sources ranging from national health care data to clinical trial data depending on the addressed evidence uncertainty.	All FIMEA's HTA reports include a chapter on PLEG. FIMEA assess new hospital-only medicinal products.	The experience in using PLEG in reassessments, managed entry agreements and decision making is very limited.	Lack of standard processes in using PLEG in decision making Quality of and timely access to real world data

NOAC: nonvitamin K antagonist oral anticoagulants; PCSK9: proprotein convertase subtilisin/kexin type 9; MEA: managed entry agreement; CtE: commissioning through evaluation; NHS: National Health Service; AIFA: Agenzia Italiana del Farmaco/Italian Medicines Agency; FIMEA: Finnish Medicines Agency; NICE: National Institute for Health and Care Excellence; RIZIV-INAMI: Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/Institut national d'assurance maladie-invalidité/National Institute for Health and Disability Insurance; TLV: Tandvårds-Läkemedelförmånsverket/Dental and Pharmaceutical Benefits Agency; ZIN: Zorginstituut Nederland/National Health Care Institute); ATMP: advanced therapy medicinal product; HAS: Haute Autorité de Santé/French National Authority for Health.

TABLE 3 Examples and uncertainties suitable for postlicensing or postlaunch evidence generation (PLEG) advice. This not a prescriptive or exhaustive list

Status of PLEG	Objectives of PLEG	Examples
Advice timing: premarketing authorisation application		
PLEG anticipated by developer while defining clinical development plan	Pharmacovigilance activities	Advice on risk management planning—proposed important identified and potential risk, pharmacovigilance plan, and risk minimisation measures
	PAES	Advice on potential postauthorisation effectiveness study, discussion on feasibility assessment, biases, target groups and relevant endpoints
	Conditional MA planning	Advice on evidence in terms of efficacy and safety, postlicensing, to convert to a full MAA for treatment
	Long-term follow-up	Plans for long-term monitoring of both safety and efficacy
	Comprehensive planning	Advice on the postlicensing plan (ongoing clinical studies, routine pharmacovigilance, real-world prospective data on effectiveness, and pharmacoeconomic data
Advice timing: perimarketing authorisation application		
PLEG anticipated peridecision making	Qualification or advice procedure	Qualification of the core data elements to be collected in a registry or safety study postlaunch[41]
Advice timing: after marketing authorisation granted		
PLEG imposed by regulators	PAES	Advice on studies on effectiveness to confirm external validity of pivotal data, parameters of study design
PLEG imposed by regulators, advice after MA	PASS category 1	Advice on long-term RCT, with an active comparator followed by an extension study, on specific safety issue
	PASS category 1	Advice on design of a noninterventional safety study deriving from a registry according to an agreed protocol
	PAES annex II	Advice on PAES commitment to investigate the efficacy in elderly patients in RCT
	PAES annex II	Advice on proposed prospective observational cohort study is designed to analyse the effectiveness in real-world settings
PLEG required by regulators	PASS category 3	Advice on an interventional study to determine incidence and severity of a specific adverse drug reaction in patients treated with combination treatment
		Advice on an observational study of the interpretability and accessibility of education materials for health care professionals and patients
		Advice on an observational study to evaluate incidence of discontinuations due to the specific adverse drug reaction in patients receiving treatment in a patient support programme
		To demonstrate long-term immunogenicity and effectiveness for a vaccine
PLEG recommended by regulators	PAES	Advice on an open label pragmatic, prospective, interventional study to further explore the long-term effects of treatment on symptoms and disease complications

(Continues)

TABLE 3 (Continued)

Status of PLEG	Objectives of PLEG	Examples
PLEG voluntary by developer		Advice on the concept and data package needed to amend the restriction of the hospital setting use Adequacy of evidence-generating needed programme to modify risk mitigation measures The acceptability of a pragmatic trial, with a standard of care comparator, to assess effectiveness To collect further data in population subgroups Prior or postinitial assessment, line extensions
Imposed or upon request by HTAs for reassessment	Advice at national level	Description of patient characteristics, mode of use of the drugs (including impact on health care organisation) and therapeutic strategies that could impact product on the long-term effectiveness of the product Comparative long-term clinical and economic data
Imposed or upon request by payers at national level regarding HTA-only specific uncertainties	Advice at national level only	Evaluation of budget impact of the drug in real condition of use with size of the treated population, treatment duration, usage in combinations, dosage, compliance Monitoring long-term effectiveness and cost-effectiveness in the context of conditional coverage.

RCT: randomised controlled trial; PASS: postauthorisation safety studies; PAES: postauthorisation efficacy studies; MA: marketing authorisation

randomised trials with secondary data collection can be complex. The section above on previous PLEG requests, highlights challenges with use of RWD in the form of registries have been observed. Seeking qualification of RWD analytical techniques, qualification of data sources or novel designs incorporating RWD in PLEG plans is possible. Qualification, a form of advice that is independent of a particular product, will provide guidance or a regulatory opinion on a particular new method for a specific intended use in the context of research and development into pharmaceuticals.[45] The EMA initiative on patient registries also aims to support the usability of registry data in regulatory decision-making.[26] To improve the quality of registries for HTA use, EUnetHTA developed the Registry Evaluation and Quality Standards Tool.[46] This tool has been created to support consistent evaluation of the suitability of registries for HTA and to address HTAb concerns about the reliability of registry data. See supplementary material 1 for further international good practice guidelines dedicated to generation of RWD.

3.1.3 | Understand regulators', HTAb' or payers' expectations from PLEG in the context of CMA discussions

PLEG proposals are best considered in the context of the pivotal programme for licensure or HTA assessment, where the suitability and feasibility of the proposal to address the objectives can be gauged and which data could be generated pre- *vs* postlaunch.[44,47,48] In EMA, Scientific Advice has been sought on such suitability of product development plans for CMA[20] with 11% of EMA Scientific Advice procedures in 2015 containing CMA-related questions. In these advice submissions, developers pose questions frequently about the justification for the CMA route and the suitability of data submission at the initial CMA stage. It is strongly recommended that the development programme is planned in its entirety prior to consideration of whether CMA might be a viable option. As per the EU Guidance on CMA, all Scientific Advice requests relating to CMA should contain a thorough discussion on PLEG, and what data could feasibly be provided to decision makers to complement the initial CMA data package, and in what timescale. This leads to a more complete discussion of expectations regarding the overall data package including timing. In such cases, engaging in multistakeholder advice will bring in wider perspectives on the expectations of other decision makers for specific proposal in this setting. Final decisions on the licensing pathway are taken at the stage of MA by the regulator.

3.1.4 | Contend with multiple stakeholders and global developments

It is acknowledged that with varied decision makers, and global pharmaceutical development, there can be multiple and sometimes conflicting demands for evidence generation. Multistakeholder advice giving simultaneous feedback on proposals will ensure that the developers are aware of what is needed for each stakeholder. This affords

the opportunity to streamline or reconcile the evidence generation to meet the needs of the different stakeholders e.g. obtaining agreement on research questions, which data might be generated only after launch, common data elements for PLEG, principles of study designs and/or aligning on the most suitable data sources. Furthermore, questions on the usability of PLEG generated in non-EU settings can be posed to European regulators if accompanied by a justification that this could be a sound approach to answer the specific uncertainty.

3.2 | Which products to target for PLEG advice

Potentially, any product may need PLEG; however, products with novel mechanisms of action, with justifiably limited development plans before initial product licensing and launch, which target rare diseases or are advanced therapies, represent areas with a greater likelihood of uncertainties following licensure or appraisal and thus a greater likelihood for PLEG requests from both Regulators and HTAb. PLEG advice may also be relevant and of benefit for new vaccine formulations. Seeking advice is also recommended when study sponsors are considering innovative approaches for evidence generation, including novel data sources or methods.

3.3 | Timing and content for PLEG advice

There are multiple factors that may influence the time when advice on PLEG can be sought, such as the time of identification of uncertainties. These may be identified by regulators[5,7,42–44] or HTAb[49] during Scientific Advice or in the course of the MA or HTA review respectively. The level of detail for a prospective plan should be as high as is feasible but will vary depending on the stage of product development. Additionally, in some cases, no predetermined timing will be possible as safety signals requiring investigation can arise de novo postlicensing and require regulatory input.

When considering interacting with HTAb on PLEG, developers should be aware that some members of Early Dialogue Working Party such as Haute Autorité de Santé and Agenzia Italiana del Farmaco participating in consolidated parallel consultation with EMA, are willing to give PLEG advice only if the developer has already sought advice on the pivotal trials, to ensure PLEG complements the prelaunch clinical development plan in the appropriate manner with evidence that could not have been developed prelaunch. In general, the content of the advice submission on PLEG from the applicant should contain enough information to discuss the research question, the study design and the quality of the data source proposed. See Supplementary material 2 for recommended content in an advice submission. Seeking advice can be broadly divided into early, peridecision-making and postdecision-making. See Figure 2. These are explored further below.

3.4 | Early PLEG advice

Early PLEG advice means advice on PLEG at any stage while the product is still in development; pivotal studies are pending, ongoing or completed, but the product is not yet submitted for marketing authorisation.

The preferred timing for early advice is once data are available from phase II trials, although this is not essential in all cases. For HTAb, ideally discussion on PLEG is part of the discussion on pivotal trial designs and related anticipated gaps in evidence. The EUnetHTA Early Dialogue Working Party could also accept advice requests on PLEG while pivotal trials are ongoing and before MA submission if pivotal trials have been previously discussed in a parallel consultation procedure.

During earlier product development, the proposals for PLEG are likely to be high level, broad and less defined than later in development when further knowledge of the product has been acquired. Early advice on PLEG may also help to identify the decision points when important issues will become clearer and when further dialogue on PLEG would be useful. The timing for further interactions may vary depending on the stage of product development and the characteristics of the product and disease but further iterations of the evidence generation plan, and repeated dialogue with regulators/HTAb on

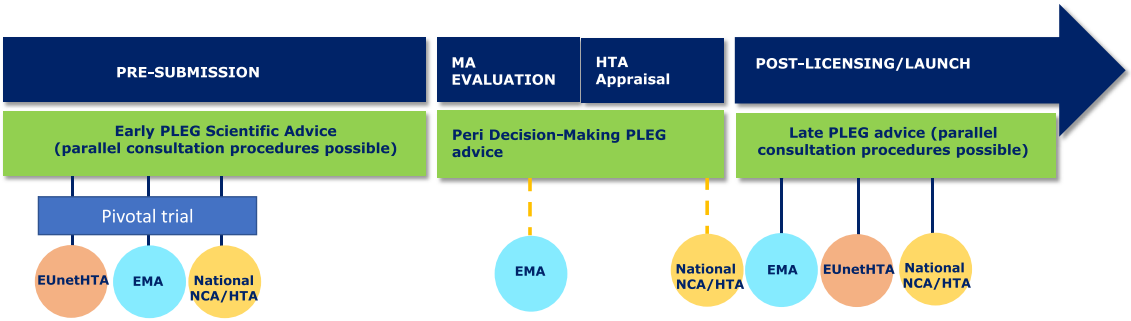

FIGURE 2 Options for seeking European regulatory or HTA body advice on PLEG according to stage of development, which are discussed in this paper. Solid line: Subject to validation/prioritisation criteria. Broken line: Case by case justification. EMA: European medicine agency; EUnetHTA: European network of health technology assessment; PLEG postlicensing or postlaunch evidence generation. MA: Marketing authorisation; NCA: National Competent Authority; HTA: Health technology assessment

PLEG may be needed. However, in the context of parallel consultations with EUnetHTA, more than 2 advice procedures for the same product are not feasible. While the first should concern the global development, the second can focus on refining PLEG initial advice. Follow-up procedures for standard EMA advice are not limited in number.

Prior to undertaking an early PLEG advice, it is recommended that developers anticipate which evidence gaps will be most critical in the regulatory or HTA context for their product at the time of MA or HTA, and plan how to address these. In an early PLEG advice, the developer puts forward the PLEG proposals as to how the anticipated gaps could be filled together with the strengths, weaknesses, feasibility or issues associated with different implementation options together with a justification as to the potential impact of the missing data at time of approval or reimbursement, and why it can be justified to collect such data postlaunch. Where possible, the design of the postlaunch study, the core set of data to be collected and data sources to be used are expected.

3.5 | Peridecision-making advice

Peridecision-making PLEG advice means that a product is going through marketing authorisation assessment, or reimbursement appraisal at the time advice is sought. It is acknowledged that this period is complex, resource-intensive and focused on answering questions for the respective procedure. During this period, considering in-depth proposals for PLEG study designs as part of the authorisation procedure is challenging. However, for highly anticipated and novel products addressing unmet needs, peridecision-making advice could be possible in order to ensure a reviewed PLEG protocol for swift implementation postlaunch. An accelerated advice procedure to meet MA timetables can be envisaged if justified in the case of such products with a briefing document focused on the PLEG proposal. Parallel consultation in this setting, whilst desirable to streamline evidence generation, may be difficult if HTAb have not yet been able to draw upon appraisal findings. Nevertheless, in a recent example, qualification of the core data elements to be collected in a registry postlaunch (Cellular therapy module of the European Society for Blood and Marrow Transplantation Registry)[41] took place at the same time as the MAs for the relevant products (CAR T-cells) were undergoing assessment, and it was possible to include HTAb as observers in the qualification procedure. This could also be the case, when a PLEG advice is needed postauthorisation but before reimbursement appraisals are completed.

3.6 | Late PLEG advice (advice postdecision making)

In this setting, both authorisation (initial or extension of indication) assessment and reimbursement appraisal are completed. However, the time available to seek advice may be short given the need to start evidence generation to ensure early implementation and availability of evidence for regulatory or health technology reassessment.

EU regulators will accept a PLEG advice application alone or in parallel with HTAb, postauthorisation, but emphasise that post-licensing studies, which are feasible, ethical and well designed to answer the uncertainty, should start without delay.

From an HTA perspective, PLEG requests to developers could be a mix between evidence for HTA reassessment and evidence relating to pricing and reimbursement decisions. Therefore, seeking input on a national level might be needed at this stage in the lifecycle of a medicine. However, seeking parallel consultation after national appraisal procedures have been completed would also be an option. PLEG proposals are expected to be detailed at this stage. As stated above, seeking advice as early as possible during the development of a medicine is the preferred option of HTAb.

3.7 | PLEG advice processes

Which route of advice to take is the developer's choice depending on priorities; input can be sought from regulators only, HTA only or from both in a parallel, setting although any legal obligations to submit the final protocol in particular cases for final regulatory committee endorsement must also be complied with.

3.7.1 | For regulators

There are several procedural routes that can apply to PLEG protocols depending on timing and the desire to include other stakeholders. Scientific Advice, which is voluntary and nonbinding, is possible throughout the lifecycle of the product, and PLEG advice can be sought via existing procedures.[50] If similar uncertainties are raised or expected by EMA and Food and Drug Administration (FDA), then parallel EMA–FDA advice can be requested by developers.[51] Postauthorisation measures are PLEG that have been agreed by an EMA committee; they are classified into the legal framework under which they will be enforced, and administered. For example, protocols of non-interventional imposed PASS have to be submitted to, assessed and endorsed by the EMA Pharmacovigilance and Risk Assessment Committee following provisions in Article 107n-o of Directive 2001/83/EC. Imposed efficacy studies may carry an obligation to submit final protocols for committee review as postauthorisation measures. However, in preparation for such submissions, developers can seek preparatory Scientific Advice. EMA technical guidance should be followed in all cases.[6,7]

3.7.2 | Regulatory and HTAb

Multistakeholder advice usually includes EU regulators and HTAb as a parallel consultation, or EU regulators and FDA. Developers need to consider which stakeholders would best meet their needs in their specific context. In parallel consultation with HTA and Regulators,[52] the EUnetHTA Early Dialogue Working Party selects products for consolidated parallel consultations on the basis of the potential of the product to bring added benefit to patients, and thus prioritises those products incorporating a new mode of action for the indication,

targeting a life-threatening/debilitating disease *and* addressing an unmet medical need. PLEG proposals, which include objectives involving potential gaps in clinical evidence or assessing relative value for regulatory and HTA are most suited for parallel consultation at the EU level. Any clinical content in scope for standard Scientific Advice with EU regulators is suitable for parallel consultation from the regulatory perspective.

3.7.3 | HTAb

EUnetHTA multi-HTA early dialogues[53] on evidence generation plans, or national HTAb with or without National Competent Authorities consultation can be an option in countries where national advice procedures are in place (France, Germany, Sweden, UK, Italy).

3.7.4 | NITAGs

Additional considerations apply in the case of vaccines because of different public bodies involved in making recommendations in this field; collaboration between regulators and NITAGs to facilitate the conduct of postauthorisation studies on safety and effectiveness of vaccines that meets needs of the different groups in the frame of a multi-stakeholder advice procedure could be foreseen. To date, there has been only 1 pilot procedure involving EU regulators, NITAGS and HTAb. Further applications from vaccines developers for such pilot procedures are encouraged.

4 | DISCUSSION

This paper particularly focuses on the rationale for seeking advice on PLEG, how, when and for which products to pursue such advice, and expectations from a regulatory and HTA perspective. It aims to present reflections based on first experience, with a view to facilitating further product-specific discussions in this area. We acknowledge that there are open questions on this topic due to the limited use of advice on PLEG so far, such as those discussed below.

4.1 | Potential barriers amongst developers to seeking PLEG advice

Currently, there are no data quantifying the scope and significance of obstacles that might deter developers from seeking advice on PLEG. However, several potential barriers have been raised within the author group.

It can be hypothesised that developers may be focused on achieving approval or reimbursement or managing constrained resources to deal with the respective applications, and thus not seek PLEG advice. This may be an issue for timing of advice but would not exclude obtaining advice on PLEG at an earlier stage. In addition, where advice has already been sought on pivotal studies, an advice procedure and briefing document focused on PLEG only may be possible.

Another related concern may be assigning resources to PLEG or PLEG advice preparation before the potential success of the product is clear. Nevertheless, it is acknowledged that there are uncertainties for all stakeholders at the time of early advice, but this presents an opportunity to design a programme to reduce uncertainties and for the developers to understand the potential PLEG commitment as far as is possible, bringing this information into strategic decision making, and employing a life-cycle perspective of evidence that is generated as a continuum.

In addition, developers may have underlying concerns that seeking such advice may result in an unmanageable burden of PLEG. The experience so far based on known PLEG advice procedures does not support this view. Lastly, vaccines developers wishing to pursue multi-stakeholder advice do not yet have any established framework or guidance, and need to contend with a variety of public bodies involved. Experience from the establishment of parallel consultations for other medicinal products provides a model. Pilot test procedures are instrumental for engendering new ways of working, developing mutual understanding and gaining the experience to inform such guidance and frameworks.

4.2 | How best to predict evidence gaps or potential uncertainties that will need PLEG

The output of Scientific Advice cannot prejudge the outcome of the marketing authorisation assessment or reimbursement appraisal, nor finally determine what the remaining uncertainties will be at that time as determined by regulators or downstream decision-makers. Early PLEG advice can lead to important signposts to developers on the existence and nature of the likely evidence gaps (e.g. long-term efficacy/safety data), and feedback on the proposal to address the gap (e.g. a registry-based study).

Developers are encouraged to target those products for advice that will be likely to result in PLEG with presentation of anticipated uncertainties on safety and efficacy. Such a gap analysis requires critical and objective judgement on the part of developers based on accumulating data, scenario planning and a willingness to acknowledge the need for life cycle evidence generation.

4.3 | Measuring the impact of PLEG advice

Measuring the impact of PLEG advice is desirable. However, there are challenges, notably the absence of comprehensive baseline data on PLEG implementation times, and multiple complex factors relating to product access could affect PLEG implementation aside from Scientific Advice. Thus, a comparison of products with and without PLEG advice would not be meaningful. The level of PLEG advice activity could, however, be tracked and characterised. Applicable studies should be registered under the clinical trial legislation or the EU PAS Register.[54] The impact of advice could possibly be assessed initially by recording time to postlicensing study start, and compliance with advice could be assessed.

This will allow documentation of methods and timelines and comparison of results and objectives. In the longer term, when the evidence has been generated and submitted for assessment, the quality

of the evidence generated, success in addressing the uncertainty, fulfilment of obligations and impact according to regulators and HTA respective remits would be desirable. Learnings from all stages of the process should be transparently fed back into the system for continuous improvement while respecting confidentiality policies. A range of next steps are proposed to enable PLEG advice in Box 3.

4.4 | Future research opportunities

This review paper has considered the experience to date of PLEG in Europe and the role it currently and is anticipated to play. However, much more research is needed to evaluate practice in PLEG not only across regulatory, HTAb and payers, but also across all stakeholders (e.g. healthcare professionals, patients, policy makers). In addition, PLEG is developing in countries and regions around the world, and as the terms and methods for PLEG are establishing, there is potential for divergence, some of which may reflect contextual need but, in any case, deserves assessment.

BOX 3 Potential actions needed to facilitate PLEG and PLEG advice.

- Share best practices in PLEG including the process for obtaining advice and the operational, technological and methodological aspects of using real-world data.
- Qualification of data sources and methods for PLEG will provide an important opportunity to increase the utility of real-world data in PLEG scenarios.
- Monitor the impact of PLEG not only within Europe, but across different regions, particularly given the collective value of these data and studies to establish a global evidence base for a medicine or other types of healthcare interventions. Measuring the impact can support a feedback loop to improve future planning so that methods and approaches that work become the norm and mistakes are not repeated.
- Continuously collect data and information on the advice process so that the format, process and timing of PLEG can be optimised.
- Further develop the process for delivering joint advice on PLEG in the periauthorisation phase.
- Develop methodology to study efficacy and effectiveness in the postlaunch phase, particularly concerning confounding factors.
- Increase the access to and analysis of real-world data in the EU to support robust decision-making, noting, however, that PLEG includes experimental and observational data.
- Align evidence generation to ensure the best use of the available data and the resources where possible, given that medicine manufacturers are developing their medicines to address global need; future efforts to gather communities of experts in this area to map out the role and use of PLEG are needed.

PLEG: postlicensing or postlaunch evidence generation, EU: European Union

5 | CONCLUSIONS

In principle, PLEG is complementary to pivotal licensing/reimbursement data and can strengthen knowledge and information on a product to resolve uncertainties related to clinical and economic outcomes and the use of the product in daily practice, contingent on appropriate study designs, and high-quality data, capture, management and analyses. PLEG can take different forms with a wide array of designs, data sources and objectives to answer remaining uncertainties from regulatory and HTAb. There is a strong rationale for medicinal product developers to seek advice on PLEG, for well-targeted products or where evidence gaps are anticipated, as part of lifecycle planning activities to optimise evidence generation. See Box 4 for key messages by sector. Therefore, product specific proposals for PLEG advice as early as possible in the development are welcomed by regulators and HTAb. Developers should seriously consider this opportunity to obtain feedback on their PLEG proposals.

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2. Have been involved in drafting the manuscript and revising it critically for important intellectual content.

BOX 4 Key messages from different sectors.

Regulators' key messages

- PLEG should complement the understanding of a medicinal product's benefit–risk profile. Having a robust plan for PLEG is important at the time of marketing authorisation application and increases the confidence of decision-makers that knowledge gaps will be filled in a reasonable timeframe in the postlicensing phase. Companies who are coming for advice on PLEG should come prepared with clear questions, and proposals that are feasible in operational, technical and methodological terms. Advice on PLEG facilitates a lifecycle proactive approach to evidence generation.
- PLEG should be planned early and repeated cycles of advice, as knowledge accumulates, are likely to result in the most robust plans and therefore the most robust evidence generation.

• There are considerable unmet medical needs. Products in areas of medical need may qualify for timely patient access tools such as conditional marketing authorisation that require, by definition, efficient data collection post-licensing. Preparatory advice on PLEG may therefore support such medicines reaching the patient earlier.

HTAb key messages

• Postlaunch evidence is not a means of replacing randomised clinical trials but should be seen as complementary knowledge.

• Postlaunch evidence can clarify a product's use in clinical practice, can be a tool to provide data for market access agreements, can be a condition for a reimbursement decision or recommendation of use or, exceptionally, can support understanding of the relative value of a new product for which evidence cannot be reasonably generated before launch. The evidence generated will be reviewed by the HTAb during a reassessment or might trigger a reassessment of the product.

• Postlaunch evidence includes data generated from trials, temporary authorisation of use programmes or early access to medicine schemes or real-world data sources such as registries, medico-administrative/claims records.

• Parallel PLEG advice should be prioritised for those products with gaps in clinical evidence from clinical trials and/or clinical practice. Other PLEG cases requested for informing on a product's use in clinical practice and developed in the context of market access agreement will not be prioritised for parallel consultations.

Key messages from pharmaceutical developers

• PLEG forms part of a continuum of evidence development, complementing earlier evidence developed for licensure, and facilitating further understanding of a product's benefit/risk profile and value proposition postinitial registration or launch. PLEG advice may improve the success rate of fulfilment of obligations and commitments, and is encouraged for all types of medicines during their lifecycle but particularly for those with remaining uncertainties at the time of initial approval, which can justifiably be addressed post-licensing or postlaunch. Harmonisation of PLEG requirements and associated data standards across regions will be important for medicines developers to ensure the efficient use of data globally.

• Advice on PLEG can be sought before or after initial regulatory approval and HTA assessment. For priority products where PLEG advice may be needed during the peri-approval phase, a leaner, quicker advice process may be considered.

• PLEG advice from regulators and/or HTAb may be obtained separately or in parallel; early timing is critical to optimise drug development and patient access.

Multistakeholder key messages

• Looking at the continuum of evidence generation from development through to the real-world setting supports decision making by various players and should be discussed prospectively.

• Seeking joint advice i.e. advice between medicines regulators and health technology assessment bodies or other stakeholders holds the promise to optimise the post-licensing/launch evidence generation plan to increase the feasibility of conducting studies and to reduce unnecessary duplication of studies.

• Use of parallel *PLEG* advice with EMA and EUnetHTA is a new and relevant tool in drug development. Increase in its use will help to address uncertainties postapproval and improve market/patient access.

EU: European Union, EUnetHTA: European Network of HTA, PLEG: postlicensing or postlaunch evidence generation, EMA: European Medicines Agency, HTA: health technology assessment, HTAb: HTA bodies

3. Have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.
4. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Bec G, Stracenski I, Castelnovo T. MAH compliance with post-authorisation: obligations in the EU: a five-year review. *Regul Rapp*. 2018;15(11):29-33.
2. Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and protecting public health: how the European Union pharmacovigilance system works. *Drug Saf*. 2017;40(10):855-869.
3. Arlett P, Portier G, de Lisa R, et al. Proactively managing the risk of marketed drugs: experience with the EMA pharmacovigilance risk assessment committee. *Nat Rev Drug Discov*. 2014;13(5):395-397.
4. Highlight report of the 4th industry stakeholder platform on research and development support. 2019; https://www.ema.europa.eu/en/documents/report/highlight-report-fourth-industry-stakeholder-platform-research-development-support-23-november-2018_en.pdf. Accessed December 16, 2019.
5. European Medicines Agency. Scientific guidance on post-authorisation efficacy studies. 2016; https://www.ema.europa.eu/documents/scientific-guideline/scientific-guidance-post-authorisation-efficacy-studies-first-version_en.pdf. Accessed March 29, 2020.
6. European Medicines Agency. Post-authorisation measures: questions and answers. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-procedural-qa/post-authorisation-measures-questions-answers. Accessed March 29, 2020.
7. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP); module VIII – post-authorisation safety studies (rev 3). 2017; https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed October 19, 2018.
8. Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making: defining and using "real-world" data. *JAMA*. 2017;318(8):703-704.
9. US Food and Drug Administration. Postmarketing requirements and commitments: searchable database. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/. Accessed February 26, 2019.
10. US Food and Drug Administration. Framework for FDA's real-world evidence Programme. 2018; https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf. Accessed February 26, 2019.
11. Health Canada. Elements of real world data/evidence quality throughout the prescription drug product life cycle. 2019; https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html. Accessed May 1, 2019.
12. Nagai S, Ozawa K. New Japanese regulatory frameworks for clinical research and marketing authorization of gene therapy and cellular therapy products. *Curr Gene Ther*. 2017;17(1):17-28.
13. Kondo E, Torii M, Oba I, Okamoto M. The pharmaceuticals and medical devices Agency's approach to facilitate risk communication and its challenges. *Yakugaku Zasshi [Journal of the Pharmaceutical Society of Japan]*. 2018;138(3):307-314.
14. Mori K, Watanabe M, Horiuchi N, Tamura A, Kutsumi H. The role of the pharmaceuticals and medical devices agency and healthcare professionals in post-marketing safety. *Clin J Gastroenterol*. 2014;7(2):103-107.
15. Langham J, Floyd D. New drugs in advanced melanoma: disparities in requirements for post-launch real-word evidence in europe. *Value Health*. 2015;18(7):A435-A436.
16. Dehnen J, Petry D, Kruse F, Bercher J. G-BA conditional approvals in the AMNOG procedure: impact on HTA outcomes and Price. *Value Health*. 2018;21:S173-S174.
17. Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: the Dutch reality check. *Health Policy*. 2019;123(3):267-274.
18. EUnetHTA criteria to select and prioritize health technologies for additional evidence generation. 2012; https://www.eunethta.eu/wp-content/uploads/2018/01/Selection-prioritisation-criteria-1.pdf. Accessed October 18, 2018.
19. Claxton K, Palmer S, Longworth L, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. *Health Technol Assess*. 2012;16(46):1-323.
20. European Medicine Agency. Conditional marketing authorisation. Report on ten years of experience at the European medicines agency. 2017; https://www.ema.europa.eu/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf. Accessed October 10, 2018.
21. Bouvy JC, Blake K, Slattery J, De Bruin ML, Arlett P, Kurz X. Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005-2013. *Pharmacoepidemiol Drug Saf*. 2017;26(12):1442-1450.
22. Pacurariu A, Plueschke K, Olmo CA, Kurz X. Imposed registries within the European postmarketing surveillance system: extended analysis and lessons learned for regulators. *Pharmacoepidemiol Drug Saf*. 2018;27(7):823-826.
23. Engel P, Almas MF, De Bruin ML, Starzyk K, Blackburn S, Dreyer NA. Lessons learned on the design and the conduct of post-authorization safety studies: review of 3 years of PRAC oversight. *Br J Clin Pharmacol*. 2017;83(4):884-893.
24. Jonker CJ, van den Berg HM, Kwa MSG, Hoes AW, Mol PGM. Registries supporting new drug applications. *Pharmacoepidemiol Drug Saf*. 2017;26(12):1451-1457.
25. Carroll R, Ramagopalan SV, Cid-Ruzafa J, Lambrelli D, McDonald L. An analysis of characteristics of post-authorisation studies registered on the ENCePP EU PAS register. *F1000Res*. 2017;6:1447.
26. European Medicines Agency Patient Registries Initiative. 2015; https://www.ema.europa.eu/human-regulatory/post-authorisation/patient-registries. Accessed October 05, 2018.
27. Moseley J. Post-licensing use of real world evidence for safety and efficacy; frequency of proposals in EMA scientific advice data on file. n.d.
28. Plueschke K, McGettigan P, Pacurariu A, Kurz X, Cave A. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. *BMJ Open*. 2018;8(6):e021864.
29. Pacurariu A, Plueschke K, McGettigan P, et al. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open*. 2018;8(9):e023090.
30. Cohet C, Rosillon D, Willame C, et al. Challenges in conducting post-authorisation safety studies (PASS): a vaccine manufacturer's view. *Vaccine*. 2017;35(23):3041-3049.

31. Haute Autorité de santé (HAS). Rapport d' activité 2018 [French Health Authority. 2018 Activity Report]. https://www.has-sante.fr/portail/jcms/c_1267546/fr/publications-institutionnelles.
32. Les études post-inscription pour les médicaments. https://www.has-sante.fr/jcms/p_3113800/fr/les-etudes-post-inscription-pour-les-medicaments#toc_1_3_1. Accessed December 16, 2019.
33. Haute Autorité de Santé. Modèles de documents relatifs aux études post-inscription demandées par la haute Autorité de Santé. [model documents relating to post-registration studies requested by the French health authority]. 2014; https://www.has-sante.fr/jcms/c_1725427/fr/modeles-de-documents-relatifs-aux-etudes-post-inscription-demandees-par-la-haute-autorite-de-sante. Accessed February 26, 2019.
34. Haute Autorité de Santé. Les études post-inscription Sur les technologies de santé (médicaments, dispositifs médicaux et actes) [French health Autority. Post-registration studies on health technologies (drugs, medical devices and procedures)]. 2012; https://www.has-sante.fr/jcms/c_1191960/fr/les-etudes-post-inscription-sur-les-technologies-de-sante-medicaments-dispositifs-medicaux-et-actes. Accessed September 10, 2019.
35. Montilla S, Xoxi E, Russo P, Cicchetti A, Pani L. Monitoring registries at Italian Medicines Agency: fostering access, guaranteeing sustainability. *Int J Technol Assess Health Care*. 2015;31(4):210-213.
36. Ministerio de Sanidad, Consumo y Bienestar Social. Plan de abordaje de las terapias avanzadas en el sistema nacional de salud: medicamentos CAR. [Ministry of Health, consumers and social welfare. Approach plan for advanced therapies in the national health system: CAR medications]. 2018; https://www.mscbs.gob.es/profesionales/farmacia/pdf/Plan_Abordaje_Terapias_Avanzadas_SNS_15112018.pdf. Accessed September 9, 2019.
37. Valtermed o cómo fijar el valor de la innovación. Valtermed or how to set the value of innovation. *Revista española de economía de la salud [Spanish journal of health economics]*. 2019;14. https://www.economiadelasalud.com/pdf/V14N1/0_EDSV14N1.pdf Accessed Spetember 9, 2019
38. González J. How can we build into the system the ability to review decisions made on the basis of results? Monitoring technologies for their inclusion in the Spanish health system benefits basket. 10th anniversary of the Spanish Network of Health Technology Assessment Agencies. Towads patient and public engagement in HTA; April 28, 2017; Zaragoza
39. Gimenez E, Badia X, Gil A, Espinosa C. Innovative contracting in Spain (2010–2016). Getting more "IN". ISPOR 19TH ANNUAL EUROPEAN CONGRESS; November 2016. 2016.
40. NICE. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer. 2016; https://www.nice.org.uk/guidance/ta416. Accessed September 10, 2019.
41. European Medicine Agency. Qualification opinion on cellular therapy module of the European Society for Blood & marrow transplantation (EBMT) registry. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development#qualification-opinion---cellular-therapy-module-of-the-european-society-for-blood-&-marrow-transplantation-(ebmt)-registry-section. Accessed September 10, 2019.
42. European Medicines Agency. Draft guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products. 2018; https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-revision_en.pdf. Accessed October 19, 2018.
43. European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. 2006; https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf. Accessed October 23, 2018.
44. European Medicines Agency. Guideline on the scientific application and the practical arrangements necessary to implement commission regulation (EC) no 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) no 726/2004. 2016; https://www.ema.europa.eu/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf. Accessed October 23, 2018.
45. European Medicines Agency. Qualification of novel methodologies for medicine development. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development. Accessed May 1, 2019.
46. EunetHTA REQueST tool and its vision paper. 2019; https://www.eunethta.eu/request-tool-and-its-vision-paper/. Accessed June 14, 2019, 2019.
47. Hofer MP, Jakobsson C, Zafiropoulos N, et al. Regulatory watch: impact of scientific advice from the European medicines agency. *Nat Rev Drug Discov*. 2015;14(5):302-303.
48. Willame C, Baril L, van den Bosch J, et al. Importance of feasibility assessments before implementing non-interventional pharmacoepidemiologic studies of vaccines: lessons learned and recommendations for future studies. *Pharmacoepidemiol Drug Saf*. 2016;25(12):1397-1406.
49. EUnetHTA JA3 work package 5 – life cycle approach to improve evidence generation. https://www.eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/. Accessed October 23, 2018.
50. European medicines agency guidance for applicants seeking scientific advice and protocol assistance. 2017; https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf. Accessed February 28, 2019.
51. General principles EMA-FDA parallel scientific advice (human medicinal products). 2017; https://www.ema.europa.eu/en/documents/other/general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf.
52. European medicines agency and EUnetHTA parallel consultation with regulators and health technology assessment bodies. 2017; https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies. Accessed February 28, 2019.
53. EUnetHTA multi-HTA early dialogues for pharmaceuticals. https://www.eunethta.eu/services/early-dialogues/multi-hta/. Accessed Febroary 28, 2019.
54. The European Union electronic register of post-authorisation studies (EU PAS register). http://www.encepp.eu/encepp_studies/indexRegister.shtml. Accessed Accessed June, 24 2019.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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