

PVA recommendations

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK

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Be brave to say no, be ethical to say yes. Drug companies have to accept saying no to some [evidence] requests, but they have to accept saying yes to some important ethical questions.

HTA leader¹

Executive Summary

Health systems are under increasing pressure throughout Europe as the ongoing fiscal crisis leads to reductions in health spending and negative consequences to patient care. In parallel, pharmaceutical manufacturers are facing increased evidence requests and the rising cost of medicine development. Since 2012, a Working Group comprising health technology assessors (HTAs) and reimbursers, medicine developers, clinicians, patient advocates and health outcomes researchers dissatisfied with the status quo has come together to determine how best to address uncertainty regarding the value of a new medicine that remains at the time of the medicine's launch. [Please see Appendix 1 for a list of PVA Working Group participants.](#)

Uncertainty concerning a medicine's value may affect decisions regarding its use and reimbursement, which in turn can delay or prevent patient access to potentially valuable treatments. Post-launch value assessment (PVA) can provide an alternative to denial of reimbursement until all evidence gaps are filled or, on the other end of the spectrum, reimbursement without a mechanism in place to fill key evidence gaps. Working Group participants defined PVA as the process by which the value of a medicine (or medical technology) to all constituents is weighed and adjusted to reflect an evolving understanding of its benefit to patients and healthcare systems over its life cycle.

Working Group participants believe a well-functioning PVA system will provide significant benefits to patients, health systems and healthcare innovators. The opportunity to generate evidence about a medicine in use will make timely access to valuable treatments possible. The continuing fiscal crisis in Europe heightens the need for progress on this issue as reimbursement authorities, facing funding constraints, increasingly call for clear evidence demonstrating the value of new treatments.

The Working Group's PVA recommendations are designed to make reimbursement decisions less "black and white." They provide companies with a framework that supports constructive discussion with regulatory and reimbursement decision makers and addresses lingering uncertainty that can be resolved post-launch. PVA can help reduce decisions not to cover a medicine at the time of reimbursement review while acknowledging the difficulty of removing products from formularies once access has been granted.

Application of the Working Group's recommendations promises to reduce duplication of evidence requests and to improve utilisation of existing healthcare information technology (IT) infrastructure, thereby lowering costs and increasing efficiency. PVA can also confirm clinical

¹ This document reflects the use of a modified version of the Chatham House Rule, whereby names of participants and their affiliations are a matter of public record, but comments made during discussions are not attributed to individuals or organisations. Quotes in italics are drawn directly from comments made by members of the Working Group.

benefit while increasing society's public health knowledge about a disease. However, PVA cannot eliminate the critical need for evidence development and stakeholder engagement during pre-launch clinical trials and should be reserved for a minority of medicines that would most benefit. PVA should be directed towards those areas of uncertainty that can effectively be addressed through means of additional data collection.

While the Working Group did not include regulators, subsequent discussions revealed a significant opportunity to apply the PVA recommendations to both reimbursement and regulatory needs.

The remainder of this document sets forth the Working Group's seven recommendations for how PVA can clarify a medicine's value and maximise health outcomes during a time of austerity across Europe. The seven PVA recommendations follow:

- Industry and health systems² should systematically address uncertainty about a medicine that is present at the time of launch when it is cost-effective, timely and realistic to gather evidence that helps inform future decision making.
- Industry and health systems should address significant remaining uncertainties if they affect decisions about access, price or role in treatment pathway.
- Industry and health systems should co-ordinate and, where possible, align regulatory and HTA evidence needs across countries to make efficient use of limited resources.
- Industry and health systems should develop and use common healthcare IT infrastructure³ for evidence gathering where possible.
- Industry and health systems should use pricing approaches that recognise both an upward and downward change in a medicine's value based on the results of post-launch research.
- Industry and health systems should use PVA to understand the differential value of a medicine across patient populations and indications. Industry and health systems should track and reflect these differences in price, access and use decisions.
- All stakeholders should continue to focus evidence development on pre-launch clinical development programmes due to the limitations of post-launch evidence generation.

Tapestry Networks will be piloting the Working Group's recommendations in the second half of 2013 and into 2014. Participants called for real-world demonstrations of effective PVA and agreed that conducting medicine-specific pilots is the logical next step to explore the practicality and value of PVA. Likely candidate medicines for PVA pilots are the minority of medicines that require post-launch studies to confirm or further demonstrate value.

² The term "health systems" is defined as all stakeholders who are involved in evaluating, prescribing and using medicines, including HTAs and payers, regulatory authorities, clinicians and patients.

³ The term "healthcare IT infrastructure" is defined as any tool used for the collection of evidence such as registries, observational databases, healthcare integrated electronic medical records, patient reported outcomes reports, administrative claims databases and health surveys.

The fiscal crisis increases pressure to confirm the value of new medicines

The fiscal crisis has reversed the post-war trend toward increasing investments in health. From 2000 until 2009, Europe's health expenditure rose steadily at an average per capita rate of 4.6% per year in real terms.⁴ This rate of increase allowed health systems to keep pace with the increasing needs of an ageing population and incorporate advances in healthcare technologies. In the first years of the crisis, many countries protected public healthcare budgets. However, health spending per capita fell by 0.6% in real terms across the European Union in 2010,⁵ with nearly all European countries reducing growth in expenditures or making outright cuts. This contraction in health system spending is unlikely to be reversed in the near future.

The global economic downturn has also had a significant effect on the European pharmaceutical industry. Austerity measures led to healthcare spending cuts in Portugal, Italy, Greece and Spain, delaying payments for some medicines for up to three years. Additionally, declines in pharmaceutical sales were down 2.2% in France, 3.1% in Italy and nearly 9% in Spain in 2011.⁶

Steering scarce resources towards the highest value medicines

As healthcare systems across Europe confront growing cost pressures, budget-holders are increasingly focused on steering resources towards high-impact interventions that deliver the best health outcomes at the lowest cost. Doing so successfully requires an understanding of how a medicine performs in clinical practice or the "real world" and is contingent upon a health system's ability to deliver the expected benefits from using a medicine under routine conditions.

For example, the French National Authority for Health (HAS) chair Jean-Luc Harousseau has stated that reimbursement rates will be reassessed shortly after a medicines' launch based on "real-life" data.⁷ The Italian Medicines Agency (AIFA) has created a new platform to streamline post-marketing assessment to ensure greater efficiency and more appropriate use of new medicines.⁸ In parallel, the European Medicines Agency (EMA) recently announced that its online register of post-authorisation studies on medicines, the European Network of Centres for Pharmacoeconomics and Pharmacovigilance (ENCePP), has reached a milestone after the uploading of its 100th study since 2010.⁹

Generating evidence comes with a cost

The need for greater evidence from pre-launch clinical trials is raising the cost of medicine development. Recent estimates suggest the cost of developing a novel medicine can approach

⁴ Organisation for Economic Co-operation and Development, *Health at a Glance: Europe 2012* (Paris: OECD Publishing, 2012), page 10.

⁵ *Ibid.*

⁶ Andrea Ornelas, "Recession-hit Nations Owe Pharma Firms Billions," Swiss Info, 25 February 2012.

⁷ "French Drug Ranking System to Reassess Reimbursement up to Three Years Post Launch," *APM Health Europe*, 13 September 2012.

⁸ "Italy Upgrades Post-marketing Assessment Systems for New Drugs," *APM Health Europe*, 26 April 2013.

⁹ "Europe's Post-Authorisation Safety Register Reaches 100-Study Milestone," *APM Health Europe*, 16 April 2013.

€1 billion.¹⁰ In addition, the EMA has steadily increased its requirements that drug developers conduct post-approval research. It is estimated that more than three-fourths of new pharmaceutical and biological product approvals in Europe come with postmarketing conditions attached to them.¹¹ Of those requiring studies, the average number of postmarketing studies is 10.8 per new drug.¹² These studies can be expensive; some estimate an average cost of €4 million per clinical postmarketing study since the 2000s, with a wide variance in cost depending on the nature of the study.¹³

Despite these investments, post-launch research often fails to further society's understanding of a medicine. In 2007, Tufts Center for the Study of Drug Development (Tufts CSDD) conducted a survey on postmarketing studies. Sixty-eight percent of the clinical study sponsors and 79% of non-clinical study sponsors believe that postmarketing study results have contributed either marginally or not at all to their understanding of the safety, efficacy or quality of a new product.¹⁴

The rising cost of developing new medicines is also due to the continued need to incorporate the evidence needs of reimbursement authorities including HTAs and payers earlier in the development process. A company's failure to generate the necessary evidence to inform country-specific market access decisions can lead to less favourable coverage decisions. This "cost of failure" from incomplete evidence and the resulting impact on a coverage decision must then be borne by subsequent medicine development programmes.

Ultimately, rising costs without commensurate benefits can limit the introduction of potentially valuable treatments to the long-term detriment of patients and society. It is in the common interest of all stakeholders to focus post-launch evidence generation on critical uncertainties to aid decision making and further knowledge about a medicine. It is in the interest of all parties to ensure that post-launch requests are fulfilled as efficiently as possible to ensure that scarce resources are deployed in ways that generate the most value.

The benefits, limitations and application of PVA

PVA should be directed towards the minority of medicines possessing areas of uncertainty that can effectively be addressed through means of additional data collection. The benefits, limitations and situations calling for PVA are described in the following sections.

¹⁰ Pharmaceutical Research and Manufacturers of America, *PHRMA Industry Profile 2012* (Washington, DC: Pharmaceutical Research and Manufacturers of America, 2012), page 31.

¹¹ "Postmarketing Studies are Becoming the Norm in U.S., Europe, and Japan," *Impact Report*, Tufts Center for the Study of Drug Development, Vol. 10, No. 4, July/August 2008, p.1.

¹² Ibid.

¹³ Christopher-Paul Milne, "Economic Argument for Comprehensive Approaches: What Studies are Being Funded?" 2013 Post-Approval Summit (Boston, MA), Harvard Medical School, 7-8 May 2013.

¹⁴ "[Postmarketing Studies Contribute Little, Study Finds.](#)" *PharmaTimes*, 31 May 2007.

The benefits of PVA

Not everything is known or can be known by regulators and reimbursement authorities at the conclusion of clinical trials. Decision makers with a low tolerance for uncertainty may simply deny reimbursement, thereby preventing patient access to new medicines.

The Working Group recommends introducing flexibility into the system through structured, systematic engagement. PVA makes it possible for patients to access new treatments while industry generates necessary evidence to address any significant lingering uncertainties that hinder decision making. This represents a path out of the “no evidence, no access” conundrum.

Importantly, health systems applying PVA need to acknowledge the impossibility of addressing each and every knowledge gap that exists at the time of launch. PVA must be linked to a life-cycle model of evidence generation that begins well before the launch of a medicine. Health systems must also recognise the significant uncertainty introduced through the use of a medicine in a less-controlled real-world setting. For example, physician and patient adherence to treatment guidelines will vary much more in a real-world setting than they do in carefully controlled clinical trials. The right application of PVA represents an opportunity for all stakeholders to come together and improve patient outcomes. PVA can be an effective vehicle to ensure a drug delivers its full promise.

While health systems must recognise these limitations, industry must recognise that authorities dislike uncertainty and will have little tolerance for evidence gaps at launch that could have been filled. A scenario that is likely to be unacceptable to many decision makers is that the developer did not want to spend the necessary money to inform payer decision making where a payer feels that the company should have addressed the evidence gaps in clinical trials. Additionally, industry pricing at the threshold of cost-effectiveness will by definition drive up cost-effectiveness uncertainty.

The limitations of PVA

Any application of PVA requires the necessary healthcare IT infrastructure to enable effective post-launch studies; across Europe, this infrastructure often does not exist or has limited capabilities. Additionally, frontline healthcare workers may lack the time or necessary incentives to enter post-launch data. Importantly, post-launch requests can ultimately fail to deliver additional value for the following reasons:

- **Methodological challenges.** When a drug is used in common practice, it is often impossible to assess value at the level of evidence and certainty that payers and other relevant healthcare stakeholders require (i.e., payers’ strong preference for randomised controlled trials over observational studies).
- **Timely generation.** Evidence must be generated when it is still relevant to decision makers. While pricing strategies for pharmaceutical companies are complex, the price of a medicine does not usually increase as more evidence is gathered after launch. Evidence may become irrelevant if it is generated after the standard of care changes or after the introduction

of a generic substitute. Therefore, post-launch studies must produce evidence in a timely fashion if they are to influence care within an appropriate time frame.

- **The regulatory label often determines the course of further research.** For any medicine, health systems need to know optimal dosage, titration, starting and stopping rules, and the hierarchy of treatment options. In most instances, it is very difficult to understand how to best use a medicine once it has been approved. Initial use of a medicine is determined by its regulatory label. It is then challenging to systematically study treatment regimes that differ in dosage or duration from those approved on the regulatory label as clinicians may lose clinical equipoise.

For the above reasons, the vast majority of questions that stakeholders are likely to have at or after launch must be anticipated early in the life cycle of a drug so they can be addressed in the pre-launch period.

Situations calling for PVA

PVA is useful when the level of uncertainty surrounding a new medicine interferes with decisions on access, price or role in the treatment pathway provided that there is a reasonable expectation that the uncertainty can be reduced by means of further timely evidence collection. Below are some examples of instances in which PVA is warranted and valuable:

- A medicine is in a poorly understood disease area for which fully validated surrogate endpoints and long-term outcome measures have not yet been developed.
- There is a need for real-world effectiveness data that could not have been generated before launch.
- There are clinical trial results with small patient populations and additional studies are needed (e.g., orphan diseases and emerging approaches to anti-microbials).

During Working Group discussions, many examples of post-launch studies that failed to add valuable insight about a medicine or to impact decision making emerged. In effect, such requests add cost to a healthcare system without generating any benefit. The Working Group recommendations summarised below suggest the possibility from a more co-ordinated, constructive and effective post-launch system. [For a summary of initiatives related to PVA, please see Appendix 2.](#)

Working Group recommendations

The Working Group believes that the following seven recommendations for PVA will deliver significant benefits to patients and those who serve them:

Recommendation 1:

Industry and health systems should systematically address uncertainty about a medicine that is present at the time of launch when it is cost-effective, timely and realistic to gather evidence that helps inform future decision making.

The Working Group developed a PVA decision framework for addressing uncertainty that can be present at the time of a medicine's launch. The decision framework covers the following elements:

- ? What decisions do reimbursement authorities need to make at the time of launch?
- ? What is the uncertainty surrounding the decisions?
- ? What evidence is required to address the uncertainty, and can this evidence be realistically generated to guide important future decisions?
- ? What approaches make it possible to generate the required evidence for a reasonable investment and within a time frame that means the evidence will still be relevant for decision making (e.g., prior to a change in the standard of care or a generic entry)?

Recommendation 2:

Industry and health systems should address significant remaining uncertainties if they affect decisions about access, price or role in treatment pathway.

Post-launch evidence generation should aim to inform reimbursement and clinical-use decisions and remove the uncertainty that hinders these decisions. As a payer participant commented, *“There’s no point studying an endpoint that won’t change a decision that has been made. There’s no point studying something if there is no intention of changing price or changing access status.”* In other words, there is value in post-launch evidence collection only if there is an expected consequence. Any request for post-launch data should be based on a clear hypothesis of how evidence will impact access, price or role in treatment decisions.

While the Working Group's focus has been on reimbursement decision making, regulators are focused on safety and the need to confirm the risk-benefit ratio post launch. When possible, regulatory and reimbursement needs should both be considered in a PVA process.

Recommendation 3:

Industry and health systems should co-ordinate and, where possible, align regulatory and HTA evidence needs across countries to make efficient use of limited resources.

Engaging and aligning regulatory and HTA requests can make the best use of limited post-launch resources by reducing duplication and using common infrastructure. The EMA has an important role in determining the post-launch agenda as it requires post-launch commitments as

a condition for licensing. Significant health system savings could be generated if HTAs and regulators could agree on the pressing post-launch questions that must be collectively addressed for a new medicine. One fruitful area for potential co-ordination is research into relative clinical efficacy and effectiveness.

While co-ordination would help in the area of relative clinical efficacy and effectiveness, there are many areas of uncertainty specific to a health system's context that cannot be addressed by evidence from outside that health system. For example, local uncertainty may emerge regarding cost-effectiveness, utilisation tracking and budget impact.

PVA can be applied within a national healthcare system as a structured approach to addressing local uncertainties that a reimbursement authority faces (please see Recommendation 1). PVA can also be applied more broadly across multiple healthcare systems and stakeholders as a means of better co-ordinating evidence generation and infrastructure use, lowering costs and increasing the utility of studies. For example, the EMA now has the power to require post-authorisation efficacy studies (PAES), while in parallel HTAs request real-world effectiveness studies. The EMA is seeking to understand how efficacy changes in everyday medical practice and what evidence there is of variability of benefit in sub-populations. If these requests can be made synchronously, the system may be able to reap the benefits of improved co-ordination. We discuss two potential applications of PVA in more detail starting on page 10.

Recommendation 4:

Industry and health systems should develop and use common healthcare IT infrastructure for evidence gathering where possible.

Most Working Group participants support common platforms for evidence capture and the broad sharing of data from post-launch studies. They believe stakeholders should avoid creating product-specific, country-specific or time-limited registries that are not effectively linked to broader healthcare IT infrastructure. An HTA participant explained, “[*Limited registries*] don't give any added value to the system as they are focused solely on the decision regarding that specific product, at the specific time.” Instead, most participants support “*multi-stakeholder registries and multi-company registries.*”

Moreover, existing registries developed to track utilisation need to be upgraded if information about the effectiveness of a therapy is also desired. Tracking both utilisation and outcomes would improve understanding on the heterogeneity of patient response and suggest further areas of study. However, clear challenges remain in determining data access and governance privileges for “common” data. Who owns data? Who has access? Who can communicate results from evidence? An upfront agreement when setting post-launch commitments is necessary to limit later confusion and loss of value.

Recommendation 5:

Industry and health systems should use pricing approaches that recognise both an

upward and downward change in a medicine's value based on the results of post-launch research.

Health systems' willingness to adjust a medicine's price, access and use based on the results of post-launch studies is an important incentive for investment in knowledge development.

Drug prices in Europe, with few exceptions, only move downwards after launch. HTA participants in the Working Group acknowledge that this limits decision-making options: *"The only direction we are able to go at the moment, because of price rigidity, is effectively to restrict access. If there was some price flexibility, you could ensure broader access."* In effect, adjusting a medicine's price, access and use based on the results of post-launch studies rewards the additional information generated about the value of a medicine in a specific real-world setting.

Recommendation 6:

Industry and health systems should use PVA to understand the differential value of a medicine across patient populations and indications. Industry and health systems should track and reflect these differences in price, access and use decisions.

Additional complexity in PVA decisions arises from the need to manage differential value across patients and indications. Some medicines have markedly different effects on different patients – a fact that has become more evident with the growth of personalised medicine and its targeted therapies. The result is that the same medicine can have different value for different populations. This effect is even more pronounced when the same medicine can be used for different indications. Prime examples occur in oncology, where the same biologic may work with different degrees of comparative effectiveness depending on the patient, the indication and available treatment alternatives.

Without a health system's acknowledgement and reward of differential value, there can be incentives across stakeholders that lead to access only in high-value indications. While noting the administrative complexity of pricing based on differential value, Working Group participants believe it could create superior incentives for evidence development and broader patient access than undifferentiated pricing. An HTA participant summarised the approach: *"You could see that you reimburse for a specific price if you have first-line usage or second-line usage, or usage [by] a specific age group. You can actually affect how a product is used if you develop this strategy."*

However, most health systems do not regularly practice differential pricing. The Working Group supports recognition of medicines' differential value across patient populations and indications. Health systems that wish to reward differential value with differential pricing will need to track carefully the utilisation of these medicines.

Recommendation 7:

All stakeholders should continue to focus evidence development on pre-launch

clinical development programmes due to the limitations of post-launch evidence generation.

Although PVA has many virtues, it is not an alternative to a well-run clinical development programme. The burden of evidence generation remains with the pre-launch clinical development programme, which is the most effective means of generating robust evidence.

The act of gathering additional post-launch evidence carries a cost, whether in higher launch expenditures, delayed access for some or all patients, transaction costs to negotiate, administer and validate agreements to help remove uncertainty, or the cost to frontline healthcare workers and patients who must input data to satisfy post-launch needs. Ethical, methodological and cost factors add to the difficulty of addressing uncertainty after licensing approval. In general, post-launch evidence should be requested only when the benefits of resolving uncertainty clearly outweigh the costs of gathering further evidence.

Post-launch value assessment is an evolving paradigm as medicine development shifts from a “tollgate” model of regulatory and reimbursement assessment to multiple points of engagement over the lifecycle of a medicine. Effective PVA systematically considers payer and reimbursement evidence needs much earlier in the medicine development process.

A pharmaceutical company ultimately drives the medicine development process through the design and execution of clinical trials and engagement with regulators and reimbursement authorities. While the responsibility for an effective evidence generation is distributed across a healthcare system, a pharmaceutical company leads the development programme. Therefore, pharmaceutical companies have an important role in engaging other stakeholders to further develop and initiate this new model of post-launch value assessment.

A call to pilot the Working Group’s recommendations

At the conclusion of the third Working Group meeting, participants called for real-world demonstrations of effective PVA. Participants agreed that conducting medicine-specific pilots is a logical next step in exploring the practicality and value of PVA.

Two potential approaches to testing the PVA recommendations

Medicine-specific pilots to determine effective post-launch commitments could be conducted either prior to or immediately following regulatory authorisation. Pilots could also be done long after launch when new uncertainty emerges (e.g., in light of a new comparator).¹⁵

- **Pre-authorisation pilots.** There is often an opportunity to agree on what information will be generated post launch prior to regulatory approval. At this time, it is still possible to further tailor pre-launch evidence development programmes. Additionally, there is an opportunity to seek input on regulatory and reimbursement needs, enabling alignment on post-launch evidence gathering.

¹⁵ The CAVOD (Clinical Value for Orphan Drugs) project is examining how to exchange evidence on effectiveness of an orphan drug throughout different stages of development.

- **Post-authorisation pilots.** Applying the PVA decision framework to resolve uncertainties that remain after regulatory approval can help to drive country-specific agreements during market access negotiations. However, it is quite challenging to co-ordinate multiple countries and stakeholders during such negotiations. There is often a small target window (approximately six months) between licensing authorisations and market access negotiations; this window opens after regulatory post-launch commitments have been determined.¹⁶ Applying the PVA Working Group recommendations in this context is likely best done by individual companies on a country-by-country basis to address an individual country's uncertainty.

Emerging characteristics of pre-authorisation PVA pilots

Pre-authorisation PVA pilots should have the following characteristics:

- **Involve the European regulatory authority and reimbursement agencies from multiple countries.** The EMA recently acquired the authority to require the generation of post-launch data on effectiveness. Additionally, the label issued by the EMA becomes an important driver of reimbursement decision making. PVA pilots should consider the mutual needs of the EMA and HTAs where their needs overlap.
- **Include other relevant stakeholders.** A PVA pilot may also benefit from participation from frontline healthcare workers responsible for inputting post-launch information. Patient representatives might be needed to speak to appropriate patient involvement and interests. Finally, it may be valuable to include healthcare IT specialists who understand the capabilities of existing or needed healthcare IT infrastructure.
- **The EMA's scientific-advice process is a useful channel for reaching PVA agreements.** Where common interests exist between regulators and HTAs, a pragmatic approach to launching PVA pilots is to engage the EMA through the already-existing scientific-advice process. Reimbursement decision makers and other key stakeholders can participate by invitation from a company requesting scientific advice. This approach has been used successfully in multi-country, multi-stakeholder early-advice proceedings. Delegates from the Scientific Advice Working Party could join Pharmacovigilance Risk Assessment Committee (PRAC) delegates to represent the regulatory perspective. Just as current advice channels offer constructive feedback in relatively short time periods, it should be possible to outline high-level agreements on post-launch requirements in a single focused session.

¹⁶ European Commission, *Proposal for a Directive of the European Parliament and the Council Relating to the Transparency of Measures Regulating the Prices of Medicinal Products for Human Use and Their Inclusion in the Scope of Public Health Insurance Systems* (Brussels: European Commission, 2013). The revised European Commission's "Transparency Directive" was published on 1 March 2012 and aims to repeal the 1989 Directive. It calls for shorter maximum time limits for completing and publishing pricing and reimbursement decisions. The range has been lowered from 180 days to 120 days for innovative products, but for more complex procedures, the 180 day-limit continues to apply. The range has also been lowered from 180 to 30 days for generic medicinal products (when the reference product has already been approved or is already included in the national health insurance system). The Directive is now subject to debate within the European Parliament and the Council of Ministers. If adopted, implementation is expected to begin in 2014.

- **Leverage the regulatory dossier.** Draft elements from the regulatory dossier, supplemented with materials needed for reimbursement decision making, could serve as the fact base for a pre-authorisation PVA pilot. Some additional preparatory work would be required to align on the key areas of uncertainty and determine a potential path (e.g., specific evidence, studies and infrastructure) to address this uncertainty. Agreements emerging from a PVA pilot discussion should ideally be recorded as a reference document for all participants.

Pilots will test the Working Group's recommendations

Clearly stated goals are critical to the success of any pilot project. PVA medicine-specific pilots will have several objectives:

- **Contribute meaningful knowledge about the value of a medicine while informing future decision making.** If the evidence gathered post launch fails to contribute meaningful knowledge about a medicine or fails to influence a future decision, the PVA pilot will not have met its objective.
- **Support successful access agreements.** PVA promises less “*black-and-white*” reimbursement decisions. In the words of an HTA representative, “*Success for my institution is to enable patients to have access to medicines. We want to be the organisation that provides healthcare to people.*” A company can engage in a constructive discussion with regulatory and reimbursement decision makers to develop further evidence that addresses uncertainty. This should help limit occasions when reimbursement authorities decide against covering a medicine at the time of review. While many factors can prevent the coverage of a new treatment, including overly aggressive pricing and poor Phase III trial results, PVA pilots must support informed access decisions, or else they will merely add to the cost of medicine development and research.
- **Lower the cost of post-launch evidence generation.** As noted previously, the cost of developing and launching a medicine continues to increase. Further adding to this cost by requiring expensive post-launch studies will result in fewer potentially valuable medicines reaching patients. In contrast, lowering the cost of post-launch evidence generation supports the objectives of contributing knowledge without placing an undue burden on companies or health systems.
- **Increase alignment across stakeholders and countries to reduce duplication of post-launch studies and infrastructure.** To reduce study duplication, stakeholders should co-ordinate evidence needs and, where possible, agree on common or shared approaches. Sometimes shared approaches across countries and stakeholders will be possible and beneficial (e.g., in cases of fundamental clinical questions on benefit and long-term outcomes). At other times, countries and stakeholders will need to go at it alone (e.g., when determining country-specific budget impact or cost-effectiveness for a treatment). Greater utilisation of existing data and of existing infrastructure will further increase efficiency. Central disease and multi-company registries, along with existing electronic medical/health record systems, should be leveraged in the pursuit of these efficiencies.

- **Confirm the value of applying the PVA decision framework.** After the conclusion of multiple pilots, Tapestry will interview public agency and company participants to learn the value they derived from the PVA pilots. We will publish summary findings as a road map for other public agencies and companies that seek to replicate this process. Ultimately, a successful effort could lead to the creation of official channels to support PVA, much as earlier work to expand scientific advice led to more expansive scientific advice being available through the EMA.¹⁷

Ultimately, it is pharmaceutical companies that develop medicines and request advice from other stakeholders. While all stakeholders acknowledge the cost of post-launch evidence generation across the health system, it will be pharmaceutical companies that initiate the PVA pilot process to address the post-launch evidence needs of specific medicines.

Candidate assets

Candidate medicines for pre-authorization PVA pilots require post-launch studies to confirm or further demonstrate the value of the medicine. Medicines that follow a well-trod development path (e.g., recent additions to a well-established class of treatments) or that have limited uncertainty are not good candidates for PVA pilots. In such cases, the cost of conducting post-launch studies beyond routine safety surveillance would likely exceed the benefits to patients and society.

However, medicines with a likely or pending conditional regulatory approval could represent one prospective class of PVA pilot candidates. Such medicines address seriously debilitating or life-threatening diseases where comprehensive clinical data has yet to be generated. These medicines must have a positive benefit-risk balance and address an unmet medical need, and there must be a reasonable expectation that comprehensive clinical data will be provided in the future. Reimbursement authorities face difficulties when evaluating medicines that have been conditionally approved because of evidence gaps in the face of significant unmet medical need.

For pre-authorization pilots, international co-ordination can be helpful to address questions about the long-term health outcomes of a medicine or where generating sufficient evidence requires enrolling patients from multiple countries.

The Working Group suggested these issues might manifest in the following disease areas. This is not intended to be an exhaustive list of valuable PVA applications.

- **Orphan medicines.** Orphan treatments are those developed to treat rare diseases, so by definition they have been tested on only a limited number of patients. Frequently, such treatments require registries that track utilisation and outcomes information. This is a more significant issue for orphan medicines as a result of the relatively fewer number of patients with rare diseases living across Europe. For orphan medicines, there is significant value from co-ordinated international data collection. By sharing information across countries, orphan medicines can increase their evidence base for subsequent post-launch analysis. Some orphan

¹⁷ Tapestry Networks, "[Pilot Consultations: Greater Engagement among Stakeholders Improves Drug Development.](#)"

conditions (e.g., Fabry disease) may have multiple product-specific patient registries that further fragment outcomes data within already-small patient populations. PVA could help align this infrastructure and study of outcomes.

- **Chronic diseases.** A medicine to treat a chronic disease such as multiple sclerosis or type 2 diabetes can rely on a surrogate or intermediate endpoint due to difficulty and expense of measuring long-term outcomes in clinical trials. A PVA process would align countries and stakeholders on firmer endpoints that track long-term benefit post-launch.
- **Oncology.** Uncertainty about the extent of the treatment effect on a specific outcome can be particularly high when therapies demonstrate significant additional benefit on other key endpoints in clinical trials, leading to an early termination of the comparative phase of the study (“cross-over between the trial arms”). Allowing patients to cross-over and to access the experimental therapy based on a specific pre-defined endpoint severely limits the ability to comparatively evaluate other long-term outcomes. Thus, some of the most promising medicines from clinical trials might also have significant levels of uncertainty about their comparative longer term impact.

Additionally, there are many occasions when a single oncology treatment can be used in multiple patient populations, indications and combination treatments. A PVA pilot could consider how to reflect a medicine’s differential value across patients and indications. This would require identifying what utilisation tracking infrastructure is necessary within and across health systems.

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Working Group participants believe that PVA can unlock tremendous value in service of patient care. Piloting the Working Group’s recommendations will allow reimbursement authorities and medicine developers to fill knowledge gaps about a new treatment without delaying access to patients who stand to benefit. One healthcare expert summarised the challenge and opportunity: *“The key word is leadership, because if this group doesn’t do it, I don’t see anyone else who will.”* Tapestry Networks will be working to implement the PVA recommendations in the second half of 2013.

About Tapestry Networks

Tapestry’s mission is to advance society’s ability to govern and lead across the borders of sector, geography and constituency. We form working partnerships that include the public and private sector as well as civil society. The participants in these networks are leaders from key stakeholders who realise the status quo is neither desirable nor sustainable. Tapestry Networks is built on the premise that relatively small groups of well-positioned leaders, seeking a goal that transcends their own parochial interests and which benefits everyone, can make progress towards that goal through the collaborative network-based approaches that Tapestry designs and leads.

Tapestry has used this network approach to address critical and complex challenges in healthcare, corporate governance and financial services – areas where private and public interests clearly

meet. Over 200 non-executive directors from over 50 of the Fortune Global 100 companies participate in our corporate governance networks. Non-executive directors, CEOs and top management from over 35 of the largest financial institutions participate in our financial services work. In healthcare, we have a track record of moving from diverse and divergent perspectives amongst senior decision makers across EU Member States to shared strategies, specific recommendations and real-world pilots. In all our work, we bring our close connection to the market forces through work done with senior executives across all sectors, our credibility as a trusted neutral agent for change and our deep experience of working effectively across public-private sectors to catalyse progress.

The views expressed in this document represent those of the Post-launch Value Assessment Working Group, a group of leading stakeholders from the public and private sectors committed to improving healthcare and economic well-being in the European Union and its Member States. This document is not intended to represent the particular policies or positions of the Working Group's individual participants or their affiliated organisations. This material is prepared by and the copyright of Tapestry Networks. It may be reproduced and redistributed, but only in its entirety, including all copyright and trademark legends.

Appendix 1: Post-launch Value Assessment Working Group participants

Health Technology Assessors | Payers

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- **Sarah Garner** | National Institute for Health and Clinical Excellence (NICE) | United Kingdom
- **Love Linnér** | The Dental and Pharmaceutical Benefits Agency (TLV) | Sweden
- **François Meyer** (observer from EUnetHTA) | EUnetHTA Work Package 7 | France
- **Sören Olofsson** | Region Skåne (former) | Sweden
- **Ad Schuurman** | Dutch Health Care Insurance Board (CvZ) | Medicine Evaluation Committee (MEDEV) | The Netherlands
- **Julius van Dam** | Menzis (former) | The Netherlands
- **Björn Wettermark** | Public Healthcare Services Committee, Stockholm County Council | Sweden

Ministries of Health | Regulatory authorities

- **José Asua** | Basque Office for HTA (Osteba), Ministry for Health, Basque Government | Spain
- **Huib Kooijman** | Ministry of Health, Welfare and Sport | The Netherlands
- **Teresa Molina** | Andalusian Health Technology Assessment Agency (AETSA), Health and Social Wellbeing Ministry of Andalusia | Spain
- **Paolo Siviero** | Italian Medicines Agency (AIFA) | Italy

Patient and policy advocates

- **Christine Lavery** | Society for Mucopolysaccharide Diseases (MPS Society) | United Kingdom
- **Christoph Thalheim** | European Multiple Sclerosis Platform (EMSP) | Belgium

Health economists | Subject matter experts

- **Jean-François Bergmann** | Lariboisière Hospital | Paris Diderot University (Paris VII) | France
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- **Filippo de Braud** | National Cancer Institute of Milan | Italy
- **Joan Escarrabill** | Hospital Clinic Barcelona | Spain
- **John Parkinson** | Clinical Practice Research Datalink (CPRD) | United Kingdom
- **Tomas Philipson** | The University of Chicago | United States
- **Adrian Towse** | Office of Health Economics (OHE) | University of Oxford | United Kingdom

Sponsor representatives

- **Chris Chinn** | GlaxoSmithKline
- **Ed Godber** | GlaxoSmithKline
- **Jens Grueger** | F. Hoffmann-La Roche
- **Ansgar Hebborn** | F. Hoffmann-La Roche
- **Clare McGrath** | AstraZeneca
- **Greg Rossi** | AstraZeneca

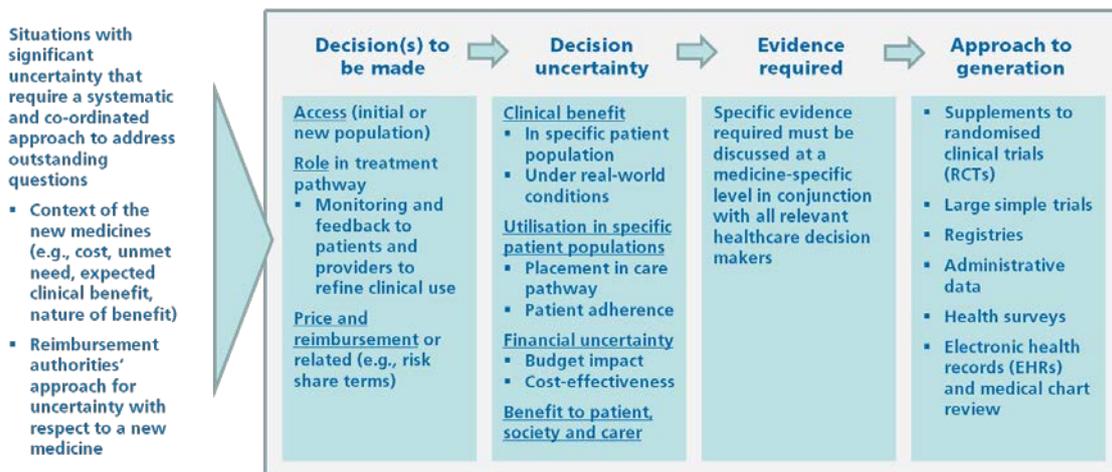
Appendix 2: Related initiatives

- **Adaptive Licensing (AL).** Similar to PVA, AL seeks to increase knowledge about the impact of a drug through targeted post-launch evidence generation and evaluation. AL also focuses on generating additional public health information and on balancing patients' access needs with the need to assess and to re-evaluate regulatory decisions. One regulatory leader asked if PVA was "*potentially very similar and complementary of adaptive licensing.*" Both acknowledge that evidence generation cannot be limited to conventional RCTs and support the role of other approaches including pragmatic clinical trials, observational studies based on electronic medical records, and registries. However, while both AL and PVA address uncertainty surrounding new medicines, AL focuses on improved benefit and/or improved safety, while PVA is more focused on access, price and role in treatment decisions core to reimbursement decision makers.¹⁸
- **EUnetHTA.** The European network for Health Technology Assessment (EUnetHTA) includes a post-launch evidence generation project within its seventh work package (July 2012) of Joint Action 2. One key deliverable is improved guidelines for further evidence generation in early dialogue with manufacturers, a goal it shares with PVA. However, EUnetHTA's approach is focused on HTAs' evidence needs, whereas PVA also seeks to address regulators' evidence needs.
- **Value-based Pricing (VBP).** Value-based pricing is a new drug-pricing approach under development in the United Kingdom that is expected to succeed the current Pharmaceutical Price Regulation Scheme (PPRS) by the end of 2013. A key principle of VBP is that the value of a medicine should be determined by its "true" or real-world value. As with PVA, such an approach will require further study of a medicine and rely on registries or healthcare IT infrastructure to collect needed evidence. However, the specifics of VBP are still being worked out.

¹⁸ For more on adaptive licensing, see H. G. Eichler et al. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval," *Clinical Pharmacology and Therapeutics* 91, no. 3 (2012), pp 426–37.

Appendix 3: The PVA decision framework

Post-launch Value Assessment decision framework



Stage 1: Decisions that reimbursement authorities must make at the time of launch

Application of the PVA decision framework begins with decisions that reimbursement authorities make at the time of launch. Participants focused on three types of decisions that would benefit from the PVA decision framework:

- Decisions about access.** Reimbursement authorities must decide whether or not to provide a given patient population access to a new medicine at a given price. They must also decide the conditions of that access. If evidence about a medicine can be gathered after the medicine is in use, then patients can gain timely access to a new treatment, and payers are no longer bound by an all-or-nothing commitment. One industry participant noted, *“I have heard many payers say that once you allow access, it is very hard to pare it back. This naturally leads payers to establish very high hurdles ... There is an opportunity [through PVA] to create much more information about a product and its budget impact in exchange for earlier access.”*
- Decisions about role in treatment pathway and optimal use in clinical practice.** PVA can be an invaluable tool for optimising the therapeutic use of a new medicine. A payer revealed, *“We never evaluate a drug; we evaluate how a drug might be used in a treatment strategy. It’s the strategies that matter.”* Challenges for PVA include questions about sequencing in a treatment pathway, dosage, titration, starting and stopping rules, and the hierarchy of treatment options. Many of the decisions that inform drug use are already set by the regulatory label. Nevertheless, using PVA to inform a medicine’s role in a treatment regime and to determine its effectiveness for that purpose improves health systems’ ability to deliver the greatest benefit to patients through the development of an optimised treatment strategy for a given medicine.

Several participants highlighted the need for a feedback loop from those generating and evaluating post-launch evidence to those using the treatments in clinical practice. This linkage is often missing.

- **Decisions about price and reimbursement.** PVA can provide the data necessary for reimbursement authorities to evaluate the value of new medicines in clinical practice. Industry participants acknowledged the need to demonstrate outcomes from their new medicines: *“In order for you to get the net prices that you wanted as a reward for innovation, you need to achieve better outcomes.”*

Stage 2: Uncertainty surrounding the decisions

At its core, the purpose of post-launch evidence generation is to reduce the uncertainty associated with key reimbursement and clinical-use decisions. The second element of the PVA decision framework highlights the fundamental uncertainty that must be addressed to inform the reimbursement decisions identified in Stage 1.

Participants highlighted four types of uncertainty that arise in the post-launch environment and hinder reimbursement and use decisions:

- **Clinical benefit in specific patient populations and/or under real-world conditions.** The actual benefit a medicine delivers in clinical practice is a key uncertainty for health system decision makers. This uncertainty encompasses both the medicine’s absolute value in a real-world setting and its relative value compared to existing treatments. One payer noted, *“You want to know the real-life effectiveness instead of efficacy in clinical trials ... You want to compare the new drug with the best existing alternatives.”* A fellow participant added that *“from a payer’s perspective, you always want to know what is the alternative and how much the alternative costs.”*

Where there are discrepancies between clinical-trial efficacy and real-world effectiveness, reimbursement authorities and clinicians want to *“find out and analyse ... the differences. Why is the data regarding post-launch effectiveness so different from the data from the clinical trials? If a drug is less effective in real life, what is the difference in circumstances? That can be patient compliance, age, co-morbidity or other things.”*

- **Utilisation.** Utilisation uncertainty concerns which patient populations are using a medicine for which indications. One HTA participant stated, *“I’m always very interested to know who’s actually getting the medicine, and for what indication. What are they not getting, or what is being displaced?”* Participants agreed that patient adherence is a form of utilisation uncertainty. Patient adherence is particularly relevant in chronic disease areas and when a medicine’s value proposition is tied to improved tolerability relative to comparators. Finally, tracking utilisation is the key to understanding and rewarding differential value.
- **Financial Uncertainty.** Post-launch evidence can address uncertainty regarding budget impact and cost-effectiveness. One payer explained, *“The question for me is the drug budget.”*

- **Benefit to patient, society and carer.** Understanding a medicine's benefit to patients, society and carers is important for reducing uncertainty regarding its value. One patient representative said that the question of the benefit to the patient *“is not automatically identical with clinical benefit,”* and added, *“What is the benefit for society? It should not be underestimated if a new drug has a value for the carer.”*

Stage 3: Evidence required to address the decision uncertainty

The third stage of the PVA decision framework focuses on what evidence is needed to fill in data gaps for reimbursement and clinical-use decisions. Ultimately, the evidence required to address specific uncertainties must be discussed at a medicine-specific level with relevant healthcare decision makers. In general, participants suggested that evidence should, as one industry participant said, provide insight into *“real-world outcomes and an understanding of how the patient, healthcare provider and the system are interacting.”*

One industry participant highlighted the centrality of evidence: *“Whether it is a question about adherence; whether it is a question about extending outcomes; whatever that question is, we have to work out where is the evidence, and how do I access that evidence.”* The participant added that evidence will help with understanding *“heterogeneity across the broad population.”*

Stage 4: Approaches that support generation of needed evidence

There are many means of generating the evidence required to reduce the uncertainties that cloud reimbursement decisions. An industry participant reminded the PVA Working Group of the need to connect studies and evidence to resulting decisions: *“Can I actually validate that this is the right method, in the right data set, with the right types of variables to be able to even answer a question?”*

We summarise below a list of approaches that the Real-World Data Task Force of the International Society for Pharmacoeconomics and Outcomes Research outlined in a recent report:¹⁹

- **Supplements to RCTs.** To provide additional data alongside standard clinically focused RCTs, researchers often gather information on variables such as patient-reported outcomes, medical resource use and costs. Supplements to RCTs can add valuable evidence on treatment patterns.
- **Large simple trials.** Large simple trials (also called practical or pragmatic clinical trials) involve prospective, randomised assignment but are aimed at a larger, more diverse real-world population. Like RCTs, these trials have the strength of randomisation, which minimises bias in the estimation of treatment effects, but by design they are larger than RCTs and therefore more likely to have the power to capture significant differences in outcomes.

¹⁹ Louis P Garrison Jr., Peter J Neumann, Pennifer Erickson, Deborah Marshall and C Daniel Mullins, [“Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report.”](#) *Value in Health* 10, no. 5 (2007), pp 326–35.

- **Registries.** Registries are prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment. Registries can be used for assessing or monitoring real-world safety and effectiveness, assessing quality of care and provider performance and assessing cost-effectiveness. They typically include a larger and more diverse group of patients than is generally studied in phase III RCTs. Therefore, they better reflect real-world patients and outcomes.
- **Administrative data.** Administrative data (typically retrospective or real-time, if possible) are collected primarily for reimbursement, but they contain some clinical diagnosis and procedure information as well. Administrative claims databases can be useful in measuring resource use and costs, as these databases lend themselves to retrospective and longitudinal and cross-sectional analyses of clinical and economic outcomes at patient, group or population levels.
- **Health surveys.** Health surveys are designed to collect descriptions of health status and well-being, healthcare utilisation, treatment patterns and healthcare expenditures from patients, providers or individuals in the general population. Health surveys typically collect information on representative individuals in a target population and are methodologically rigorous.
- **Electronic health records and medical chart review.** Electronic health records and other technologies capture real-time clinical treatment and outcomes and contain more detailed longitudinal information, including disease-specific symptoms at the individual level.