

Building a sustainable platform for multi-stakeholder collaboration

Introduction

The European Healthcare Innovation Leadership Network convened in Paris on 12-13 January 2011 for its seventh meeting. The Network has been on a multi-year journey to address the complementary goals of improving patient health outcomes and enhancing the climate for innovation, while acknowledging pressures to control healthcare costs.

The seventh meeting was designed to address the following objectives identified by Network members:

- Explore a new model of leadership and governance
- Review and discuss ongoing pilots of multi-stakeholder consultations in drug development
- Discuss the creation of a sustainable model for multi-stakeholder collaboration
- Examine a new set of Alzheimer's disease diagnostics as an example of the link between diagnostics, biomarkers and drug development
- Shape the Network's 2011 agenda

The following members and guests attended dinner before the meeting or the meeting itself:

- Eric Abadie, Direction Générale, Agence française de sécurité sanitaire des produits de santé (AFSSAPS), France
- Ron Akehurst, Professor of Health Economics – School of Health and Related Research, University of Sheffield, United Kingdom, *Guest*
- David Byrne, Former EU Commissioner, Health and Consumer Protection
- Eddie Gray, President, Pharmaceuticals Europe, GlaxoSmithKline
- Rainer Hess, Impartial Chairman, Federal Joint Committee (G-BA), Germany
- Pavel Hroboň, Former Deputy Minister, Ministry of Health, Czech Republic
- Finn Børllum Kristensen, Chairman of the Executive Committee, European network for Health Technology Assessment (EUnetHTA), *Guest Observer*
- Thomas Lönngren, Former Executive Director, European Medicines Agency
- David Norton, Company Group Chairman, Global Pharmaceuticals, Johnson & Johnson
- Anders Olauson, President, European Patients' Forum
- Sören Olofsson, Chief Executive Officer, Region Skåne, Sweden
- Ulf Säter, Regional Vice President, Europe, AstraZeneca

- Wolfgang Schmeinck, Representative of the Board, BKK Landesverband Nordrhein-Westfalen, Germany
- Ad Schuurman, Head of the Business Contact Centre, College voor zorgverzekeringen (CVZ), The Netherlands, *Guest*
- Sophia Tickell, Executive Director, SustainAbility, and Director, PharmaFutures
- Marta Wosinska, Director – Analysis Staff, US Food & Drug Administration (FDA), United States, *Guest Observer*

Several members who were unable to attend participated in discussions with Tapestry Networks in preparation for the meeting:

- Bert Boer, Executive Member of the Board, College voor zorgverzekeringen (CVZ), The Netherlands
- Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom, *Guest*
- Mike Leers, Adviser, Board of Commissioners, CZ Healthcare Insurance Group, The Netherlands
- Noël Renaudin, President, Comité Economique des Produits de Santé (CEPS), France
- Sir Michael Rawlins, Chairman, National Institute for Health and Clinical Excellence (NICE), United Kingdom
- Sir Mike Richards CBE, National Clinical Director for Cancer and End of Life Care, St Thomas' Hospital, United Kingdom
- Martin van Rijn, CEO, PGGM, The Netherlands

ViewPoints is a synthesis of key issues arising in discussions among members of the Network that also includes comments and perspectives from other subject-matter experts. It is produced by Tapestry Networks to stimulate substantive dialogue on the choices confronting healthcare leaders.

ViewPoints reflects the Network's use of a modified version of the Chatham House Rule, whereby names of members and their affiliations are a matter of public record, but comments made during meetings are not attributed to individuals or organisations. Quotes in italics are drawn directly from comments made by members and guests participating in the meeting. The ultimate value of *ViewPoints* lies in its power to help all constituencies develop their own informed points of view on these important issues. *ViewPoints* may be shared freely.

Executive summary

The seventh meeting of the European Healthcare Innovation Leadership Network brought together a senior group of healthcare leaders and guests who are pioneering new approaches for improving patient and healthcare outcomes. Members and guests discussed the progress of the

pilots of multi-stakeholder consultations in early-stage drug development, which were a recommendation of the breast cancer and type 2 diabetes working groups previously convened at the behest of the Network. The purpose of the consultations is to improve clarity and alignment among the stakeholders regarding what constitutes a medicine's value and the evidence required to demonstrate that value most effectively. Members explored how the pilots could inform a more sustainable model for multi-stakeholder collaboration. Additionally, the Network examined a new set of Alzheimer's disease diagnostics as an example of the link between diagnostics, biomarkers and drug development, and endorsed the opportunity to gain further clarity through a pilot consultation.

The following is a summary of themes from the meeting:

- **Addressing healthcare challenges through new models of leadership and governance (page 4).** Members and guests agreed that new models of leadership are needed to address increasingly complex challenges in healthcare. Members and guests recognised the relatively unique role the Network plays in *“aligning commercial and public interests to result in affordable innovation,”* an objective that no single institution or stakeholder can fully realise whilst working independently. Additionally, members highlighted the importance of moving from divergent views to convergence on a plan of action that results in progress.
- **Pilots test new leadership models to overcome critical challenges in drug development (page 5).** As the first set of pilots near completion, Network members recommended re-examining the key challenges in the drug development process that the pilots were designed to address. These challenges include the scarcity of resources available to develop high-value medicines, costly late-stage failures of new medicines in clinical trials and the varying requirements of regulators, HTAs and clinicians for approval, endorsement and uptake of new medicines. A multi-stakeholder consultation provides an opportunity for participants to direct resources to the best projects to ensure their success and to increase understanding of the requirements for each stage of the development process among all stakeholders.
- **Update on the first set of pilots (page 12).** Network members in Paris received an update on the progress of piloting multi-stakeholder consultations in early-stage drug development. Members discussed the impact of the pilot consultations on the development plans of the two companies that had already completed consultations, and the learning of other stakeholders that participated. Members also elaborated on the potential benefits of a multi-stakeholder consultation relative to existing advice processes.
- **New Alzheimer's disease diagnostics present ethical and reimbursement challenges (page 16).** Members agreed that Alzheimer's disease is a growing patient and societal challenge. Further, members discussed the implications of new Alzheimer's diagnostics for reimbursement, for future planning for patients and for scientific research. Members recognised the need for increased collaboration in Alzheimer's research and

identified the pilots as an opportunity to encourage multi-stakeholder collaboration in Alzheimer's drug development.

- **Our collective path forward and commitments to progress (page 20).** With three successful multi-stakeholder pilots nearing completion, members have high aspirations for the coming year. Members agreed on a plan of action that includes publishing the findings from the first set of pilots, conducting a second set of pilots to refine the process, and expanding the impact of this initiative to new geographies and companies. As one participant summarised: *“There is a lot of potential. There are a lot of possibilities to go on.”*

Addressing healthcare challenges through new models of leadership and governance

Members and guests who gathered for dinner on 12 January share the view that new models of leadership are needed to address increasingly complex challenges in healthcare. Growing interdependence and interconnectivity between regulatory, health technology and payer organisations driven by the need for continuing involvement over the life-cycle of a medicine has stressed existing leadership and governance structures in the healthcare system. Economic pressures arising from the global economic recession, changing European demographics and a decline in pharmaceutical research and development productivity further heighten these tensions. Members and guests said they recognise the relatively unique role the Network might play in *“aligning commercial and public interests to result in affordable innovation,”* an objective that no single institution or stakeholder can fully realise whilst working alone. Of course, the independent assessments required for a safe and effective health system must not be compromised in any way.

Network members considered the possibility that one small but committed group could serve as a model to address common challenges through individual and collective leadership. One Network member summarised the spirit of this conversation by noting the importance of *“not working in isolation ... but bringing everybody together around the table to speak with each other and understand each other because this is the basis of the future.”* However, other members remained sceptical that progress was possible and noted that there is only a *“small chance to get real leadership – but we should still try to do it.”*

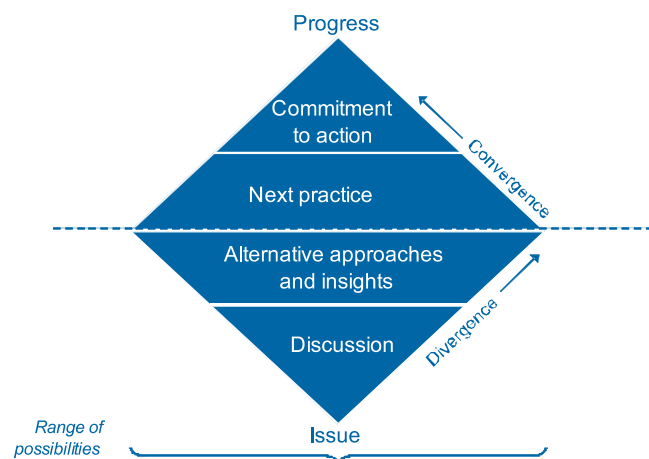
The pilots of multi-stakeholder consultations serve as a tangible demonstration project for a new model of leadership and governance that supports the collective interest of multiple distinct institutions. For example, the global nature of a single clinical development programme – which must address the varied evidence requirements of regulators, reimbursement agencies, providers, patients and payers – demonstrates healthcare complexity and interdependence; meanwhile, the development of high-value medicines to address critical unmet patient needs is an area that calls out for individual and collective leadership. The pilots represent, in the words of one guest, a *“working example to identify and address differences between us,”* ultimately developing and refining this new model in a real-world setting. As another member observed, the pilots are a way to *“avoid verticalisation ... and [give us] substance to work on.”*

Leadership requires moving from dialogue to convergence and action

One Network member observed, *“There is something immensely powerful about payers, HTAs and companies all accepting that there is a common problem that they are all required to gather around a table to solve ... this is a very powerful part of the process – do not underestimate it.”* When leaders work collectively, they can begin to understand alternative approaches and fully explore divergent points of view. A Network member summarised this journey as an opportunity to *“overcome fairly national and entrenched ideas”* and *“think about how to roll out ideas to get much more buy-in from a collective group.”*

Engaging in broad discussion to generate the best ideas may be necessary for achieving progress, but it is not sufficient. Therefore, it is critical to move from expansive but divergent discussions to a common view of the challenge and a possible path forward, coupled with individual and collective commitments to action. However, it is at this latter stage where progress often falters. The movement from divergent to convergent views requires the exercise of individual and group leadership. Exhibit 1, below, summarises this journey and serves as a frame of reference for the Network’s current activities.

Exhibit 1: Moving from discussion to action



Pilots test new leadership models to overcome critical challenges in drug development

The pilots represent a concrete move towards convergence in a multi-year effort involving over 200 European healthcare leaders. Network members have been focused on developing more differentiated market access, pricing and reimbursement solutions to reflect – and reward – the actual health and economic value delivered by different treatments.¹ Network members recognised in 2008 that moving the value discussion from abstract concepts to concrete

¹ European Healthcare Innovation Leadership Network, [“Setting the Agenda for Healthcare System Performance,”](#) *ViewPoints*, 11 December 2006.

outcomes required a disease-specific focus.² Network members and Tapestry Networks identified type 2 diabetes and breast cancer as initial focus areas for two working groups, chosen for their high unmet needs and impact on healthcare systems. The working groups established a shared value framework – an agreed set of attributes, therapeutic endpoints and economic inputs – for evaluating new medicines in these therapeutic areas.³ Participants also identified a number of challenges in the drug-development process that limit the ability of health systems to deliver the right medicines to the right patients at the right time. These challenges include the scarcity of resources available to develop high-value medicines, costly late-stage failures in clinical trials, and the varying requirements of regulators, HTAs and clinicians for approval, endorsement and uptake of new drugs. We explore each of these challenges in more detail below.

Scarcity of resources available to develop high-value medicines

A scarcity of resources for funding and rewarding innovation is being felt in the public and private spheres. An increase in the cost of developing new medicines, combined with reduced resources to pay for them, has led to decreased research and development (R&D) investment by drug developers. For example, Eli Lilly CEO John Lechleiter recently stated that many drug developers are “hedging their bets [and] reducing their focus on innovative medicines.”⁴ A senior regulator noted the scope of the problem. He said: *“we spend approximately \$60 billion every year to put on the market five or six new molecules that are first-in-class... that means that the cost of drug development is absolutely terrific, and we have to do something about that.”* An HTA leader underscored this need by noting that, given current financial constraints, *“effective new agents are appearing that we are unable to fund.”* An industry participant invoked the need for a new leadership model, through which stakeholders can *“work together in thinking about how we’re going to make investment decisions for the benefit of patients and how we’re going to link the investment to ... an appropriate value position from a regulatory and a payer point of view.”*

Tightening budgets for public agencies involved in drug development

The need to improve the efficiency of investments into the development of new medicines is particularly acute given the need for several Member States to reduce their healthcare spending. Many European countries face large deficits and tightening budgets, highlighting the need to prioritise healthcare investments by all stakeholders. For example, the UK’s National Health Service has been asked to find £20 billion of savings in the overall health budget. Similarly, Germany seeks to cut healthcare spending by €3.5 billion⁵ and France is looking to cut over €2 billion.⁶ Thus, payers *“face a decision today about how to best make use of money within limited healthcare budgets.”* Multi-stakeholder pilot consultations encourage the highest and

² European Healthcare Innovation Leadership Network, [“Aligning Perspectives on Value.”](#) *ViewPoints*, 16 September 2008.

³ See European Healthcare Innovation Leadership Network, [“Improving Health Outcomes in Breast Cancer: Recommendations of the Breast Cancer Working Group.”](#) March 2010 and European Healthcare Innovation Leadership Network, [“Improving Health Outcomes in Type 2 Diabetes: Recommendations of the Type 2 Diabetes Working Group.”](#) March 2010.

⁴ APM Newswire, “Lilly CEO Says Can Move Molecule from Candidate to Proof of Concept for \$10 Million,” 10 February 2011.

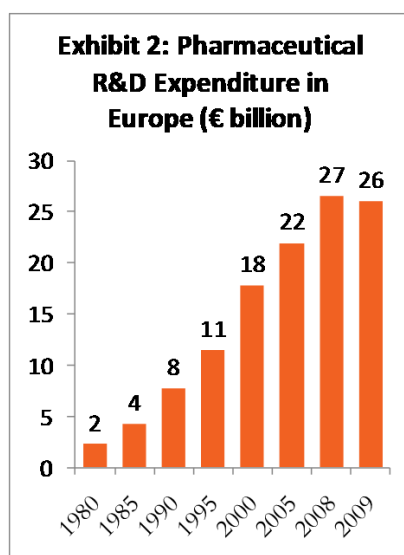
⁵ [“Germany to Raise State Healthcare Charges by 6bn Euros.”](#) *BBC News*, 6 July 2010.

⁶ [“French Government to Tackle Surging Health Care Deficit.”](#) *Reuters*, 7 September 2009.

best use of limited healthcare funds by improving the evidence available for HTAs and payers to assess the value of a new medicine clearly. A non-payer participant concurred that multi-stakeholder pilots are beneficial because “*payers get better data to base their decisions on as well as an opportunity for horizon-scanning,*” allowing payers to prepare for the introduction of a new medicine.

Additionally, the consultations being piloted allow payers and HTAs to encourage companies to focus development efforts on medicines that address critical unmet patient needs or promise to decrease long-term spending in a healthcare system. As one stakeholder commented, “*Companies often come up with ready-made solutions and ask for marketing authorisation and reimbursement ... only afterwards do they realise [that] those products did not meet specific needs or demand from payers, regulators or health authorities.*”

Tightening budgets for drug developers



The world-wide recession, coupled with declining R&D productivity, has led pharmaceutical companies to reduce their investments in the development of new medicines. A 2007 estimate of the cost to develop a new biological or chemical entity was around €1,059 million (\$1,318 million),⁷ compared with \$802 million in 2001 and \$318 million in 1987.⁸ Aggregate R&D expenditures for European pharmaceutical companies rose from €7,766 million in 1990 to €26,545 million in 2006 (see Exhibit 2).⁹ However, since 2008, relatively flat expenditures coupled with the escalating cost of clinical trials – brought on by the increasingly complex nature of science and larger trial-size requirements – are resulting in pharmaceutical companies placing fewer bets on the development of specific medicines. In Europe, investment of research-based pharmaceutical sales back into R&D programmes

climbed from 15.6% in 1985 to 20.6% in 2000, but by 2009 fell back to 17.3%.¹⁰ It is increasingly important for all stakeholders to anticipate which medicines are most needed and to focus scarce resources in those areas.

The pilots of multi-stakeholder consultations in early-stage drug development are designed to help pharmaceutical companies and other stakeholders apply limited resources towards the projects most likely to result in added value to healthcare systems. The process allows a company to gather input on a novel idea from a diverse group of key stakeholders in order to develop the most effective and efficient path forward in its development programme. An

⁷ “[A Highly Regulated Industry](#),” European Federation of Pharmaceutical Industries and Associations, accessed 17 February 2011.

⁸ “[The Pharmaceutical Industry in Figures](#),” European Federation of Pharmaceutical Industries and Associations, accessed 17 February 2010.

⁹ “[The Pharmaceutical Industry in Figures](#).”

¹⁰ “[The Pharmaceutical Industry in Figures](#).”

industry participant explained, *“As a programme progresses, decisions are made and paths are established, and once we go down a certain path it is very hard to deviate from that path. So the key purpose for an early consultation is to help us figure out the best path.”* Ultimately, placing the right bets benefits other stakeholders and society as well. As Europe spends increasing amounts of money on healthcare – from 7.8% GDP in 1997 to 8.5% in 2002¹¹ to 9% in 2006¹² – the pilots offer one way to ensure that payers and society are able to focus resources on the development of drugs expected to provide the greatest benefit.

In addition to identifying the most important development programmes, companies can seek stakeholder feedback to eliminate projects or studies that do not contribute to the assessment of a drug’s value. After hearing the stakeholders’ critical evaluation of one set of clinical studies, an industry representative commented, *“I have no problem saying that we don’t need [this specific] study. We have now taken out something that is costly and takes time.”* The participant added, *“We don’t want to end up with products or studies that no one wants to have.”* Even more fundamentally, another industry participant noted, *“What is so important to include in a consultation is dialogue with payer organisations because no one wants to spend many, many years and millions of dollars coming to the conclusion that we have a medicine that the society does not value.”* Multi-stakeholder consultations have the potential to quickly design a drug-development programme that meets the needs of multiple stakeholders.

Frequent and costly late-stage failures in drug development

Several recent high-profile late-stage failures have highlighted the need for improvements to the drug-development process to increase the likelihood of success in later stages of clinical development. The scale and cost of clinical trials increase in later stages, leading late-stage failures to have a disproportionate impact on developers and limiting resources available for investment in other promising development programmes. Network members and other participants have highlighted the opportunity to, in the words of one pilot participant, *“avoid unnecessary surprises and wastage in development programmes.”*

Late-stage failures illustrate the significant risk and reward that companies face when developing new medicines. From the laboratory to the pharmacy shelf, it takes 10 to 13 years to bring a new drug to patients. Of every 10,000 compounds that enter the drug-discovery stage, 250 will progress to the preclinical phase, 10 will reach clinical trials, and only one will receive regulatory approval for market launch; once launched, only three out of 10 medicines generate sales that match or exceed R&D costs.¹³

Half of phase III failures occur due to lack of efficacy, the demonstration of which is a primary objective of phase II trials. According to a recent report,¹⁴ two factors contributed most to

¹¹ [“OECD Reports Healthcare Spending Outstrips Economic Growth by 1.7 Times,”](#) European Public Health Alliance, last modified 26 August 2005.

¹² Bartosz Przywara, [“Projecting Future Health Care Expenditure at European Level: Drivers, Methodology and Main Results,”](#) *Economic Papers* 417, July 2010.

¹³ PhRMA, [“What Goes Into the Cost of Prescription Drugs?”](#) June 2005.

¹⁴ Maria A. Gordian, Navjot Singh, and Rodney W. Zimmel, [“Why Drugs Fall Short in Late-Stage Trials,”](#) *McKinsey Quarterly*, November 2006.

efficacy failures: (1) drugs with novel mechanisms of action failed more than twice as often as drugs using traditional ones; (2) drugs with endpoints that are perceived to be less objective, such as patient-reported outcomes, failed 10% more often than drugs with established endpoints. Drugs with both factors failed 75% percent of the time, compared to a 25% failure rate for drugs that featured neither characteristic.

Multi-stakeholder consultations in drug development could help reduce these phase III failure rates. Understanding different stakeholder perspectives early in development, one member said, *“will increase the probability of success in confirmatory trials [by facilitating agreement on parameters such as] the right dose and the right target population.”* A medical expert commented, *“It has taken an enormous length of time to get the good treatments that we have into patients, and that process, I hope, will be shortened and made more accurate.”*

Increased clarity from other stakeholders involved in assessing the value of a new medicine will improve the success rate of clinical trials, ultimately maximising the public benefit from investments in drug development. If such clarity does not emerge, one member said, *“the cost of drug development today will remain unreasonable because of the small incremental benefit of many new drugs.”*

Challenges to satisfying the requirements of all stakeholders involved in the approval, reimbursement and uptake of new drugs

Developers strive to create medicines that meet the needs of all stakeholders involved in the approval, reimbursement and uptake of new drugs. Achieving this objective, however, is complicated by the *“different responsibilities of reimbursement agencies and the registration authorities,”* which create different evidence and data demands for each stakeholder. For example, many medicines that receive licensing authorisation by regulatory authorities are not recommended for reimbursement by European HTAs. An HTA representative commented that companies may focus too *“narrowly on the acquisition of data for the purpose of obtaining regulatory approval”* since *“health technology assessment bodies and reimbursement bodies have not been very transparent about the methods they use.”* Further, even if regulators and HTAs approve a medicine, it may not find favour with payers or it might not be applied in clinical practice. A patient advocate explained, *“We see marvellous new drugs on the market but too often they are not available for patients.”* With so many different demands, another member added, *“inevitably a company can’t satisfy all of its masters and must make compromised choices.”* Ultimately, there can be only one clinical development plan, tailored to meet the needs of many disparate stakeholders. As one industry representative noted, *“If there are too many hurdles, drug development in a particular therapy area just stops.”*

After receiving significant R&D investment, many new drugs fail to receive licensing authorisation and/or a reimbursement recommendation from an HTA. For example, of 89 applications submitted to the European Medicines Agency (EMA) in 2010, 51 were finalised with positive opinions.¹⁵ Drugs with successful EMA applications then progress to a cost-

¹⁵ European Medicines Agency, [Medicinal Products for Human Use: Monthly Figures – December 2010](#), 7 January 2011.

effectiveness assessment with a reimbursement agency. Between March 2000 and November 2010, the National Institute for Health and Clinical Excellence, the HTA agency in the UK, decided to “recommend” or “optimise” (endorse with limited relevant population) 328 of 398 applications (83%).¹⁶ In 2007, the Transparency Commission, France’s HTA agency, had a reimbursement rate of 76.77% for retail pharmaceutical drugs.¹⁷

A drug that has received licensing authorisation and is recommended for reimbursement may still come under fire by payers who focus on the impact of the drug on budgets. For example, payers may encourage the use of a less expensive generic drug for first-line treatments and restrict more expensive brand-name drug to the second line of treatment or to smaller patient populations.

Finally, even if a drug has received licensing authorisation, reimbursement recommendation and support from payers, doctors still must prescribe it for patients to benefit. Uptake of new, innovative medicines in Europe remains slow: of total global sales of new drugs launched during the period 2005–2009, 29% of sales were on the European market, compared with 61% on the US market.¹⁸ Further, uptake is inconsistent across EU member states; for example, the UK has one of the lowest usage rates for hepatitis B and multiple sclerosis drugs, but the highest for statins for cardiovascular disease and thrombolytics to treat acute myocardial infarction.¹⁹ Thus, to be successful, a company must provide evidence to satisfy regulators, HTAs, payers, doctors and patients, all of whom fall across multiple jurisdictions with varying standards of care.

A multi-stakeholder consultation may provide a forum that would enable stakeholders to understand how evidence requirements differ by stakeholder group and by country. One participant stated, *“I think early-stage consultations can be helpful in defining the common set of objectives ... such that, at the time of regulatory authorisation, relevant data has been generated for health technology assessment as well.”*

In addition to impact on a company’s strategy to produce relevant evidence, the pilots are also designed to encourage *“regulators and HTAs ... to pose questions to industry and each other so that everyone can understand any concerns associated with a new compound.”* A regulator commented, *“For me, it’s very exciting to see how HTA and payers think and... start discussing how it is possible to satisfy the different stakeholders in the same development plan.”* Thus, the pilot process will provide an *“understanding of common areas among participant stakeholders and of where the gaps or differences remain,”* so that stakeholders may help companies more efficiently gain approval from relevant agencies.

In summary, the pilot process is designed to address three common challenges to drug development. In this way, participants hope to encourage the creation of innovative drugs that will significantly improve patient outcomes.

¹⁶ [“Technology Appraisal Recommendation Summary,”](#) National Institute for Health and Clinical Excellence, 17 December 2010.

¹⁷ International Society for Pharmacoeconomics and Outcomes Research, [“France – Pharmaceuticals,”](#) *ISPOR Global Health Care Systems Road Map*, updated October 2009.

¹⁸ [“The Pharmaceutical Industry in Figures.”](#)

¹⁹ Lynn Taylor, [“UK Lags Europe in Uptake of New Cancer Drugs, Study Shows,”](#) *PharmaTimes Online*, 28 July 2010.

Update on the first set of pilots

Network members in Paris received an update on the progress of piloting multi-stakeholder consultations in drug development. The pilots represent a milestone in an effort that arose from the Network and now involve over 200 healthcare leaders from across Europe. A pilot participant summarised the motivation for contributing to the pilots: *“in the realm of drug development the status quo is not working and is not sustainable. If we are going to succeed in the future in bringing effective and cost-effective drugs to patients, then a greater alignment and even partnership will be required between all parties to ensure that the best interests of industry, society, healthcare providers and patients are all served.”*

Initial set of pilot consultations

The first pilot consultation took place on 25 October 2010, when a team of drug developers from AstraZeneca met with EMA regulators, HTA representatives from five EU Member States, payers, medical experts and a patient representative to discuss the value proposition of a medicine under development for type 2 diabetes and how the company should go about demonstrating that value. An HTA participant remarked in closing, *“We were touched by the breath of history today as this was, to my knowledge, the first cross-border early stakeholder consultation ever to take place in Europe.”*

The 25 October meeting was the first of three pilots of multi-stakeholder consultations in drug development. A team from GlaxoSmithKline conferred with a similar group of stakeholders regarding a type 2 diabetes medicine on 2 December, and in early February 2011, a development team from Johnson & Johnson sought advice regarding an oncology medicine. The remainder of this section covers the preliminary findings from the first two pilots – a more complete review of pilot findings, including results from the third pilot, will be published in the spring.

Organisation of pilot consultations

Pilot consultations include participants from the EMA, the Transparency Commission in France, the Health Care Insurance Board (CVZ) in the Netherlands, the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden, and the UK National Institute for Health and Clinical Excellence (NICE), as well as the German Centre for Health Technology Assessment and Public Health and regional payers from The Netherlands, Sweden and the UK. Because medicines for oncology and diabetes must gain market authorisation through a centralised procedure, the EMA is providing advice through its Scientific Advice Working Party (SAWP), with the involvement of the Committee for Medicinal Products for Human Use. Medical experts and patient advocates, many of whom participated in the 2009 working groups, complete the consultation group. In addition, the Italian Medicines Agency sent a participant to the February pilot consultation. [Please see Appendix A for a list of institutions contributing to the pilot consultations.](#)

Each consultation is co-chaired by a regulatory and an HTA participant, with Tapestry Networks serving as moderator. At the start of each pilot, the sponsoring company presents participants with a briefing document that describes a medicine under development and raises a number of questions regarding its value proposition and development plan. Prior to the

consultation, clarification calls give participants the opportunity to request additional information and to help the sponsoring company sharpen its questions. The process culminates in a face-to-face consultation at which the stakeholders engage in a discussion with company representatives and amongst each other, guided by the questions raised in the briefing document. [Please see Appendix B for a more detailed overview of the pilot design.](#)

Tapestry Networks has been debriefing pilot participants following each consultation and uses the resulting information to refine the process and distil findings. Tapestry also provides participants with a set of informal minutes of each consultation.

Feedback from early experience with the pilots

At the January Network meeting, members considered the emerging themes from the two completed pilots as well as initial feedback from the third pilot, which was in process at the time. Tapestry Networks, as convenor of the pilots, is following up with each pilot participant as a way to compile the collective learning from the consultations and find ways to refine the pilot process. We highlight below aspects of the pilots that received particular attention at the Network meeting.

Measures of pilot success: impact on company development plans

Network members agreed that the most important measure of pilot success is the impact the consultations have on the sponsors' development plans for the medicines discussed. As a pilot participant and Network guest noted, *"If we want to invest in this process then we need the stories of the companies."* An industry member acknowledged that, initially, *"there was a bit of tension and nervousness on how this process would work and what would be the outcome."* In practice, however, the consultations *"will have a concrete and practical influence on the way we continue our development"* with *"tangible consequences for the development programme."* A fellow industry member agreed and noted that for the medicine his company brought to the pilot, *"the ultimate development programme is likely to be different than before the asset team went into the consultation meeting."*

Members of company asset teams participating in consultations, whom Tapestry debriefed following the pilots, reinforced this perspective. They described the pilots as *"a unique and needed process resulting in genuine and constructive discussions"* that provided a *"highly beneficial opportunity to seek advice from a group representing different stakeholders on the decisions to be made early in pharmaceutical product development."*

As an example of the expected impact on development plans, an industry participant listed three areas that the company would approach differently in light of the advice received: the scientific basis for the medicine's mechanism of action and link to biomarkers, the approach to patient segmentation, and the proof-of-concept study design. Non-industry participants also welcomed the pilots as a way to increase understanding among healthcare institutions and help ensure that industry's development decisions reflect the needs of health systems.

Challenges in consulting on early-stage assets: confronting uncertainty

The first set of pilots is an experiment in informal, collaborative engagement on questions relevant to early-stage drug development. Participating industry representatives have noted that the *“preliminary nature of the discussion”* in fact reflects the degree of uncertainty they confront in making development decisions. In this early stage of development, briefing documents have less asset-specific data and asset teams ask more open-ended questions than participants who are experienced in early advice are used to. An industry leader explained, *“We are trying to become as smart as we can be as early as possible. Once the development path is set, it’s very difficult to move away from it.”* Pilot participants thus have been called on to engage in a forward-looking discussion.

Network members and guests discussed the challenges that engaging at such an early stage present for pilot participants. An industry member recounted that his company’s asset team entered the pilot consultation *“having to make decisions in 2011 with a view to a potential launch in 2016.”* For them, *“the most difficult part of the process ... was getting participants to consistently put their heads in 2016 and give them advice in the context of predictions or feelings about what the standard of care would be five years later.”* This need to be predictive calls on consultation participants *“to go out of their own comfort zones.”*

An HTA leader agreed that, to the extent that the pilots involve early-stage assets, they will require participants to confront the same uncertainties that developers face. He noted, *“I recognise the problem we have as assessors to look into the five-year future,”* and he acknowledged, *“We have to learn.”*

Benefits of the pilots relative to existing advice processes

Members and guests discussed the uniqueness of the pilot process relative to current available processes that offer insight into stakeholder thinking. Existing forums for canvassing stakeholder perspectives include regulatory scientific advice processes, the pilot of joint regulatory and HTA advice conducted by the Swedish TLV and Medical Products Agency, and the early consultation process introduced recently by NICE in the UK. Such official forums are augmented by advisory panels brought together by companies and comprising *“people not actually representatives of the bodies concerned but recently having been employed by them or being involved with them from the outside.”*

Industry members lauded the pilots for bringing together the perspectives of multiple stakeholders across member states. An industry leader noted that, while companies are able to have informal discussions with at least some pilot participants, *“the way you can do it is very different from country to country.”* In contrast, *“the uniqueness of the pilots is that they are multi-stakeholder and potentially could grow to be pan-European. In that sense they are a new form of feedback that we do not have today.”*

Another industry member agreed that in the past, opportunities for feedback have tended to be limited to a single stakeholder group. This has led to developers receiving conflicting advice: *“Whether it is across countries or even within the same country, one gets different advice*

through those consultations. And yet we face a situation that there is going to be one development programme and somehow you have to find a way to get many bits of advice into that one programme.” The pilots offer a way out of this dilemma, with this member suggesting that *“[multi-stakeholder consultations can lead to] the best and most cost-efficient development programme.”*

Members and guests at the meeting voiced an additional benefit to bringing together institutions representing multiple stakeholders: the feedback and opportunity for learning that participants can take back to their institutions. An HTA guest explained: *“what this group offers that informal advisory boards do not is the possibility of furthering and more closely aligning the way the different agencies approach the issues that arise.”* This school of thought suggests that the pilots are a means for participants to *“iterate around recurring questions of drug development”* so that, over time, they *“can collectively agree on an approach.”*

Members suggested that through this process the pilots, in an incremental way, could create a forum for healthcare institutions to move towards greater alignment with each other’s evidentiary requirements. A member with budget responsibilities explained, *“I see a lot of problems today in the lack of communication between regulatory agencies and those who make the decisions whether the drugs are to be used or not. One of the beauties with these pilots is the possibility to align better the regulatory authorities, the agencies, the HTA and reimbursement authorities with the actual thinking of payer organisations.”* An industry leader agreed, calling for further pilots: *“If we have a process that is ongoing... we can refine this process and learn from it. If we do that over time, we may find that it leads to valuable alignment.”*

From the perspective of participating institutions, the pilots provide a forum for scientific and health-economics discussions across traditional roles that can feed back into their organisations’ internal knowledge base and decision-making processes. As one HTA participant noted, the pilots present *“a learning curve on all sides and [are] a two-way flow of information between all institutions present,”* not just unilateral advice from advisers to the company. A payer supported this view and concluded that the *“pilots provided an opportunity for better cross-stakeholder understanding and really evolved my views.”*

New Alzheimer’s disease diagnostics present ethical & reimbursement challenges

One scientific area that calls out for new models of innovation and collaboration is the research and development of new therapies for Alzheimer’s disease (AD), which presents a growing public health concern with significant unmet needs. Prior to the meeting, members received a brief summary of recent progress in understanding and diagnosing AD. [Please see Appendix C for a review of the background information members received.](#) At the meeting, members explored whether public healthcare systems should pay for a diagnostic that can accurately predict who will develop AD when there is no proven effective therapy that treats the disease or arrests its progression. Members discussed reimbursement considerations in both clinical and research settings and agreed that further collaboration would be necessary in this area of critical unmet need.

Alzheimer's disease: a growing patient and societal challenge

Members noted that because of ageing European populations, AD represents a critical unmet need with a significant cost to health systems and individual patients. One member remarked, “[AD] is a tremendous problem ... because we have no cure.” European governments and pharmaceutical companies are struggling to invest appropriate resources into “complex elderly diseases” such as AD along with long-term care options for patients and families who suffer from them. “One of the problems many countries are trying to solve now is how to distinguish acute medical care from ... rehabilitation and ... long-term support. Obviously having people [assigned to incorrect] categories does not provide the right care for them and costs more.” Another member added that “long-term care ... is a big part of healthcare and it is likely to grow fastest because of population ageing.”

A payer representative, however, pointed out that a cure for AD would not necessarily reduce healthcare costs to the system: “If you assume that these patients cost a lot, if we cure Alzheimer's there would be other costs in the end for other reasons ... we create new costs because people live longer and need a lot of care.” In short, “It is difficult to say that with an invention that cures Alzheimer's we could get rid of these other healthcare costs.”

From the perspective of industry, the “lack of [understanding of the] basic science in Alzheimer's” makes investment in AD projects “high risk.” Despite the risk, “[industry] is interested in Alzheimer's. It is acknowledged on all sides as high unmet medical need and on all the projections there are going to be lots of people [affected by AD].” However, because of these complexities in elderly healthcare and ambiguity around the science of AD, the specific commercial and societal value propositions for an effective AD medicine remain unclear.

Divergent views on reimbursement for AD diagnostics

The lack of an effective AD medicine, along with lack of consensus around what value such a medicine would offer, brings into question the potential value of AD diagnostics. Newly developed diagnostic tools in AD include a non-invasive positron emission tomography (PET) scan to reveal amyloid plaques in the brain,²⁰ a blood test that evaluates 100 proteins in combination with genetic and other patient information,²¹ and a spinal fluid test that identifies the presence of beta-amyloid and tau.²² Clinicians can use these tests for accurate and early diagnosis and for predicting and monitoring disease progression, but these diagnostics may also be applied to great benefit in the research setting.

Reimbursement in a clinical setting

Members discussed whether EU Member States should reimburse for AD diagnostics in the clinical setting based on a range of associated circumstances that suggest a patient's increased likelihood of developing AD, including exhibiting early symptoms and having a family history of

²⁰ Harald Hampel et al, “Biomarkers for Alzheimer's Disease: Academic, Industry and Regulatory Perspectives,” *Nature Reviews Drug Discovery* 9 (July 2010), pp 560–74.

²¹ Julie Steenhuisen, “Simple Blood Test May Detect Alzheimer's Study,” *Reuters*, 13 September 2010.

²² Gina Kolata, “In Spinal-Fluid Test, an Early Warning on Alzheimer's,” *New York Times*, 9 August 2010.

the disease. There was a consensus view that the state should not reimburse for an AD diagnostic when a patient shows no family history or early symptoms. However, more than half of members and guests recommended reimbursement for a patient who showed a family history and early symptoms (57% agreed or strongly agreed to reimburse).

Many members commented that health systems should not pay for reimbursement of a diagnostic for a disease for which there is no effective treatment. An HTA representative noted that, in order to be reimbursed, a diagnostic *“has to have a positive effect on treatment or change [the patient’s] situation.”* A different HTA participant agreed that, with regard to AD diagnostics, *“I still have the fundamental problem [recommending reimbursement] when we will not treat a condition differently after diagnosis.”*

Other members, however, focused on the personal right of a patient to know the diagnosis and to plan appropriately for their future. In some member states, there is an acknowledged imperative to *“give the patient the clear right to decide for themselves what they want to know.”* An industry representative added, *“From my perspective, if I know in 20 years’ time I will have AD, then I have a responsibility to plan my life because I know what kind of burdens are coming on my relatives.”* Another member concurred, adding, *“If we know in advance, then maybe the planning process would offer much more cost-effective and better quality care for the patient and his relatives for the period when they have developed the disease.”*

Reimbursement in a research setting

Members concurred that biomarker research towards effective diagnostics can make an important contribution to the development of new medicines. Specifically, such research can lower development costs by decreasing clinical-trial size and length and identifying populations responsive to a new medicine. Because diagnostics in the research context have the potential for such positive impact, an HTA representative commented, *“For this type of research, it is reasonable that the society pays for [the diagnostic].”*

One member referred to a case-study demonstration of how a diagnostic can contribute to the development of a new medicine: *“[Researchers] presumed that [the HER2] biomarker had been validated when they started to develop Herceptin. The number of patients in the clinical trials were brought down from 4,000 to 400 patients [by screening for patients who would respond to a drug] ... which also reduces the time needed to conduct a trial.”* Additionally, a diagnostic test can aid in identifying responders to a new medicine, thereby increasing the drug-response rate. The member continued, *“The response rate for Herceptin increased from 10% to 50%.”*

Identifying responders informs decisions about which patients to exclude from a treatment, avoiding unnecessary exposure to a new and potentially dangerous drug. Referencing such risks, one member said, *“I as an individual really want to have the result of a biomarker before I start drug treatment to know if I belong to the responders. [The case study suggests that] the whole drug-development process could be improved substantially if [there were] validated biomarkers at the beginning of the drug-development process.”*

Members recognised the need to facilitate the validation of these biomarkers in order to reap the research benefits of the tests. One member commented on legislation in Europe and the United States with potential to encourage development of useful diagnostic tests: *“We introduced a special scientific procedure at the European Medicines Agency a couple of years ago that allowed a company to get advice on the development of biomarkers and also offered a possibility to validate biomarkers after they were developed. We have done that together with the FDA.”*

Need for more collaboration in AD drug development

Members discussed innovative and collaborative ways to face challenges in developing new treatments for AD. A senior regulator asked, *“If we have [gaps in research] areas that are commercially interesting or difficult from the scientific point of view, how can we create incentives and the demand from the political healthcare system that we need something in this area?”* While one member recognised that *“many companies have closed down their research in this area because it is difficult to get new medicines [into the pipeline],”* an industry participant explained that companies should instead *“look to [develop AD drugs] differently than we have in the past. Rather than trying to do and own everything ourselves, we are trying to spread the risk for areas of interest.”* A different industry participant observed, *“There are certainly a number of efforts that are much more collaborative than I have seen before in the industry.”* Through collaborations with public and private stakeholders, industry can more effectively *“manage the risk”* in AD drug development *“to get real benefit to patients.”*

Opportunity for a future pilot consultation focused on AD treatment

A pilot focused on a new AD treatment could provide a vehicle for a company to lessen the risk of its drug-development programme by capturing diverse stakeholder perspectives early in the development process. Stakeholders could assist industry development teams in making appropriate strategic decisions early in the development path that will produce evidence required for both launch and post-launch activities. Such collaboration could foster the introduction of a novel generation of AD medicines by offering industry the opportunity to assess multiple stakeholder perspectives simultaneously in a scientifically uncertain development area with no precedent and no comparators. At the same time, stakeholders may increase understanding of inconsistent perspectives on novel development issues and potentially develop an approach to address those inconsistencies. In summary, a collaborative pilot focused on AD could facilitate progress in an area of significant unmet medical need, which could result in significant cost savings to industry and to European healthcare systems.

Our collective path forward and commitments to progress

With three successful multi-stakeholder pilots nearing completion, spirits and aspirations are running high. One member commented, *“It is obvious that this programme and the pilots have responded to a need around us.”* An HTA representative added, *“There is a lot of potential. There are a lot of possibilities to go on.”* Members agreed on a plan of action that includes publishing the findings from the first set of pilots, conducting a second set of pilots to refine the

process, and continuing to expand the impact of this initiative to new companies and geographic areas.

Capture and publish findings from the first set of pilots

Members said they believe it is critical to document the findings from the first set of pilots and invite perspectives from pilot participants. Perspectives included calls to *“make sure that we thoroughly evaluate what was going on in the pilots”* as well for *“taking time to consolidate the pilot learnings.”* A member said, *“If we have a platform of conclusions that we can agree on, we can start to disseminate this information.”* An industry representative agreed, noting that *“the impact should [focus on] supplying scientific rigour on the outcomes [of the pilots]. That is what gives us credibility, and then when we unfold into the public we can defend our position.”*

Tapestry Networks will continue to work with Network members and pilot participants to capture and disseminate pilot findings, including the findings from the third Johnson & Johnson pilot that are not discussed in this *ViewPoints*.

Continue to refine and validate multi-stakeholder consultations through a second set of pilots

Members agreed that the findings from the first set of pilots should be applied to a second set. A senior regulatory leader said, *“We need more pilots in order to determine exactly the direction of this [initiative] in the future.”* Members focused on both participation and development issues to be addressed by this second set of pilots. Regarding participation, one pilot participant advised strong outreach to current and prospective participants to ensure their contribution to the new set of pilots: *“Do not go too fast; we have to take the others with us too. I have to do a lot of work in my organisation to convince people this is a good activity and investment.”*

Other members provided suggestions on how to ensure robust participation in the second set of pilots. One challenge is to provide an appropriate participation and resourcing model that meets the needs of the diverse agencies expected to contribute. An HTA pilot representative explained, *“It is about capacity; it is about money; it is about independence; it is about confidentiality ... We need some kind of organisation to make it easy to handle these things.”* Thus, a key objective for the second set of pilots is to develop a model that enables sustainable participation from a range of stakeholders.

Ultimately, one goal for the pilot phase is to contribute to a transitional structure supporting multi-stakeholder consultations until a permanent platform emerges. As one member explained, *“We have run a few pilots ... that benefit industry, other stakeholders and patients ... [What] we have is a prototype now, but my vision would be that it would be a more stable and continuous process than what we now have.”*

Continue to define the highest and best purpose for multi-stakeholder consultations

With regard to the second set of pilots, members discussed identifying issues in drug development that may be most appropriate for further experimentation with this unique forum.

A common suggestion was to identify issues faced by all stakeholders, such as *“certain kinds of data that we are commonly asking for and wanting.”* Additionally, members considered testing the pilot process with a later phase of the development cycle. A member noted, *“For me, a pilot consultation should include post-launch studies to have more impact as a payer.”*

While it is critical to identify areas best suited for the multi-stakeholder process, it is equally important to be aware of topics that would be better addressed in a different forum. An industry participant noted that the Network must *“make sure that what we do next is incremental and additive, and not duplicative.”* Accordingly, one clear objective for the next set of pilots will be to determine when traditional forms of bilateral scientific advice with one HTA or regulator is a preferred approach. Since a multi-stakeholder process can be more resource intensive than bilateral advice with one agency, it is important to know when engaging a broader constituency through multi-stakeholder consultations involving multiple geographic regions is more appropriate. During discussions with pilot participants, two areas emerged as particularly valuable uses of a multi-stakeholder consultation:

- **Evaluating novel and strategic development questions in early-stage medicines.** Engaging multiple key constituencies to jointly shape or validate a novel development programme can help reduce the risk of a new approach even when there is no well-trodden development track record to follow. Sample topics that might be addressed include the testing and validation of a new clinical trial endpoint or assessing the validity of a new diagnostic or biomarker. Some of the findings from this type of consultation may in fact apply across a class of products and may even be considered precompetitive, with implications that could be shared with other drug developers.
- **Identifying areas where current methods of value assessment fail to capture or reward the potential value of a new medicine appropriately.** Regulators, HTAs and payer decision-makers apply different methodologies to value assessment. When there is uncertainty and inconsistency in how key institutions assess value, it creates an environment that limits a drug company’s willingness to invest in a new medicine. Clarifying where the differences are across institutions and having stakeholders co-develop a path forward with the company (e.g., a development plan that could accommodate these major issues) would be a potential goal of this consultation. This type of consultation would likely fit a later-stage asset with significant proof of concept data already available to enable a tangible and concrete conversation about value assessment.

Expand the scope of consultations to new companies and geographic regions

Members also discussed the opportunity to include additional regions and companies in the next set of pilots. One HTA representative said, *“Two countries that I would love to see around the table are the Australians and the Canadians. They have a long history [in value assessment] ... Also, we welcome representatives of countries that have a more decentralised HTA structure within their own countries, for example the Spanish.”* Another member expressed similar support: *“We need larger geographies to be involved and I fully support Italy and Spain.”*

An industry sponsor also noted the importance of broadening participation to include *“not just new member states ... HTAs and regulatory participants but also new company participants”* so that the value from multi-stakeholder consultations can accrue more broadly and the scalability of these pilots can be tested by including broader representation from industry.

Report on the first set of pilots

Once debriefing conversations from the first set of pilots are finished, Tapestry will compile the findings in one report and invite comments from pilot participants and the Network. We anticipate distributing the report in the spring of 2011.

Conclusion

There is growing acceptance across EU member states and healthcare institutions that by working together to develop new models of leadership and governance, we can make collective progress in addressing the rising cost of medicines and the declining rate of innovation. The pilots of multi-stakeholder consultations in drug development represent a significant move towards convergence on collaborative approaches and collective action. The path forward will require clearly communicating the lessons learned from the first set of pilots, the design of a second set of pilots to continue to validate the need for multi-stakeholder consultations and evolve their value, and the development of a sustainable model for resourcing and supporting these consultations. In the words of one Network member, *“what I think would be success for us all would be to align commercial and public interests in such a manner to result in affordable innovation that meets medical need, both unmet and improved existing medical therapies.”*

The views expressed in this document represent those of the European Healthcare Innovation Leadership Network, a group of leading stakeholders from the public and private sectors committed to improving healthcare and economic wellbeing in the European Union and its member states. This document is not intended to represent the particular policies or positions of the Network's individual participants or their affiliated organisations. This material is prepared and copyrighted by Tapestry Networks. It may be reproduced and redistributed, but only in its entirety, including all copyright and trademark legends.

Appendix A: Institutions contributing to the pilot consultations

France	<ul style="list-style-type: none">▪ Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)▪ Comité Economique des Produits de Santé (CEPS)▪ Haute autorité de santé (HAS)/Commission de la Transparence
Italy	<ul style="list-style-type: none">▪ Agenzia Italiana del Farmaco (AIFA) Italian Medicines Agency
The Netherlands	<ul style="list-style-type: none">▪ CVZ (College voor zorgverzekeringen) [Health Care Insurance Board]▪ Dutch Diabetes Association▪ Menzis▪ Netherlands Breast Cancer Association (BVN)▪ UVIT
Sweden	<ul style="list-style-type: none">▪ Breast Cancer Association (BRO)▪ Dental and Pharmaceutical Benefits Agency (TLV)▪ Medical Products Agency (MPA)▪ SKL (Sveriges Kommuner och Landsting) Landsting County Councils
United Kingdom	<ul style="list-style-type: none">▪ Medicines and Healthcare products Regulatory Agency (MHRA)▪ National Health Service Primary Care Trusts (Derbyshire County, Redcar & Cleveland, Stockton-on-Tees)▪ National Institute for Health and Clinical Excellence (NICE)
Pan-European	<ul style="list-style-type: none">▪ EUnetHTA (Observer)▪ EUROPA DONNA (Observer)▪ European Medicines Agency (EMA)
United States	<ul style="list-style-type: none">▪ US Food and Drug Administration (Liaison)
Industry	<ul style="list-style-type: none">▪ AstraZeneca▪ GlaxoSmithKline▪ Johnson & Johnson

Appendix B: The design of the pilot process

Tapestry Networks designed the pilot process in close collaboration with institutional participants. This appendix provides details regarding the design of the pilot process.

Conditions for institutional participation

Ensuring institutional participation in the pilots required putting into practice a number of design principles. These principles sought to address the following challenges:

- How to ensure collaboration while maintaining role independence
- How to ensure adequate and appropriate resourcing to cover the cost of participation

We briefly address each of these below.

Ensuring collaboration while maintaining role independence

Some participants found reconciling their official mandates with participation in a novel collaborative process spanning institutional roles and geographies to be a challenge. As a starting point, participants needed to be sure that taking part in the pilots was consistent with the legal framework within which their institutions operate. Government representatives were uncertain how they should interact with company asset teams in the pilot environment, which is more informal than the existing structures through which company and government representatives traditionally interact.

To ensure consistency with legal mandates, all participants with existing early-advice processes are participating under the authority and procedures that their mandates prescribe. For example, the EMA is participating through the Agency's Scientific Advice process, and the TLV is taking part in conjunction with the MPA, the Swedish regulatory agency (through the MPA's participation in EMA committees). Given that these mandates leave much of the process details to the discretion of the agency, however, participants have had a fair amount of flexibility.

Ensuring adequate and appropriate resourcing for participants

A number of institutions requested fees to offset the time and resource commitments that participation in the pilots necessitated. As one HTA participant noted, *"We would like to take the approach of providing institutional advice, but with that, there are resource consequences."*

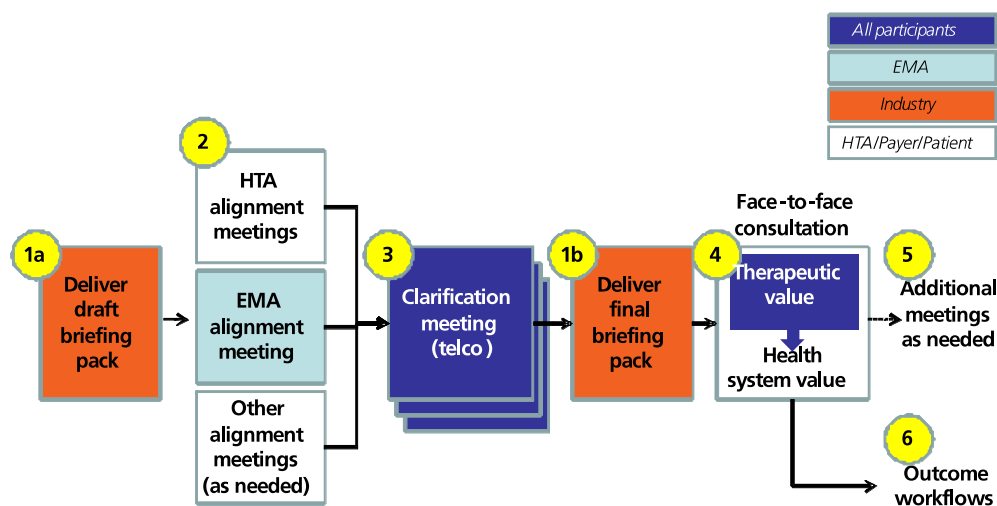
The fee requests posed two types of challenges. First, industry sponsors were concerned that the total cost of the consultation would become significant if all participating institutions required payment along the lines charged by the few agencies that currently have early-advice processes in place (particularly EMA and NICE). This concern was eased when several participating institutions waived fees in consideration of the opportunity for learning afforded by the pilots.

Tapestry Networks designed an equitable resourcing model to address the fee requests of the remaining institutions. Payment is based on a standard per diem for each participant across

institutions. To place a cap on overall expenses, participating institutions agreed to keep the total fees they charge below the level they currently charge for providing early advice.

The pilot consultation process

The graphic below presents a high-level summary of the process for multi-stakeholder consultations in drug development that emerged from negotiations with participating institutions. This process creates an opportunity for concurrent advice on issues of therapeutic value (with all stakeholders involved) and economic value (with a narrower group of HTAs and payers).



In **step 1a**, the medicine sponsor distributes a briefing document describing the asset (i.e., the medicine), its proposed value proposition and relevant available data, along with a set of questions on which the company is seeking advice to inform development decisions. In **step 2**, each participating institution reviews the briefing document and has the opportunity to seek alignment on its advice with similar stakeholders (e.g., HTAs across member states).²³

A series of teleconferences (**step 3**) provide an opportunity for participants to seek clarification of the briefing document and questions raised by the company. The discussion is also useful in providing feedback on how to structure the upcoming face-to-face consultation and prioritise the topics for discussion.

If warranted by the comments received, the sponsor company revises the briefing document (**step 1b**) and distributes it to participants. The process culminates in a half-day face-to-face consultation (**step 4**) that all participants attend. During this session, the assembled stakeholders seek to provide advice and discussion in response to the sponsor's questions.

²³ Note that, thus far, participating institutions have not pre-aligned.

The face-to-face consultations are co-chaired by one member each of the regulatory and HTA communities. Participants in the first set of pilots have decided to rotate co-chairs between consultations to provide a broader opportunity for exposure and learning. For the first pilot (AstraZeneca-sponsored medicine), Ad Schuurman (CVZ) and Kristina Dunder (EMA delegate from Sweden's MPA) served in this capacity. The second pilot (GlaxoSmithKline-sponsored medicine) was co-chaired by Minne Casteels (SAWP member from Belgium) and Peter Kolominsky-Rabas (German Centre for Health Technology Assessment and Public Health).

Participating institutions are following their customary practice – be it formal or informal – in rendering advice. For example, the EMA is adhering to its Scientific Advice process and issues its advice in written form at the conclusion of the consultation. Regardless of how participating institutions contribute to the discussion, all advice is non-binding.

The pilot process provides an option to convene additional advice meetings (**step 5**) as needed, in recognition that *“drug development is a dynamic process and science evolves.”* Tapestry Networks has been debriefing pilot participants after each consultation to refine the process for the next pilot. At the end of the pilot phase, Tapestry – in partnership with pilot participants – will distil key lessons (**step 6**) that will inform the design of subsequent pilots and other current or future multi-institutional advice processes.

Appendix C: Multi-stakeholder collaboration spurs progress in Alzheimer's disease

A set of emerging diagnostics in AD is presenting critical ethical and reimbursement challenges that will become increasingly common in the era of personalised medicine. Specifically, several members noted the challenges of *“the public paying for diagnostics when there are no effective treatments.”* Nevertheless, because *“diagnostics and their associated biomarkers are key to understanding disease progression and ultimately curing Alzheimer's disease,”* several members concluded that *“we should reimburse for diagnostics, as they help support innovation.”*

This Network previously considered developing a shared value framework for AD similar to those developed for breast cancer and type 2 diabetes.²⁴ However, Network members concluded that understanding of the disease had not advanced sufficiently to enable the development of a framework for assessing value. At the time, one member stated, *“We will not reach consensus in Alzheimer's disease because the scientific basis for consensus does not exist. Nobody understands the link between the physical or molecular changes in the body (for example, a reduction in amyloid plaques in the brain) and the basis for assessment of value.”*

The following section presents a brief overview of the economic and societal burden of AD as a case study reflecting on the promise and complications arising from a new generation of diagnostics, including their impact on the development of new medicines and new ways to assess the effectiveness of existing medicines.

A brief overview of Alzheimer's disease

AD is the most common form of neurodegenerative dementia and is particularly common in elderly populations. While the disease may first present as mild forgetfulness or occasional confusion, patients with AD experience a rapid decline until sufferers can no longer process information, understand or produce language, recognise their loved ones or perform everyday activities. Eventually this cognitive decline leads to a premature death. In Europe, approximately 50%–70% of dementia cases can be classified as AD,²⁵ and AD cases are expected to double from 9.95 million in 2010 to 18.65 million in 2050,²⁶ with one new AD case being diagnosed every seven seconds.²⁷ There is currently no known cure for AD, though some medicines do provide symptomatic relief.

²⁴ European Healthcare Innovation Leadership Network, [“Aligning perspectives on value.”](#) *ViewPoints*, 16 September 2008, pp 19–20.

²⁵ Commission of the European Communities, [Communication from the Commission to the European Parliament and the Council on a European initiative on Alzheimer's disease and other dementias](#) (Brussels: Commission of the European Communities, 2009), page 2.

²⁶ Martin Prince and Jim Jackson, eds., [World Alzheimer Report 2009: Executive Summary](#) (London: Alzheimer's Disease International, 2009), page 8.

²⁷ [Ibid.](#), preface.

Rapidly rising costs

Over 35.6 million people worldwide suffer from dementia,²⁸ and the financial cost of research, treatment and care associated with AD place an overwhelming burden on society. In 2005, worldwide AD costs were estimated at €236.5 billion per year, with the majority of those costs coming from high-income countries.²⁹ Today, the global costs have risen to €453.5 billion per year, more than 1% of worldwide gross domestic product (GDP).³⁰

The 2005 costs for patients with AD in the EU totalled €130 billion, at about €21,000 per patient.³¹ In the UK, AD patient costs skyrocketed from approximately €14.6 billion in 2004 to €25.5 billion in 2009, twice the costs of cancer (€13.3 billion), three times those of heart disease (€8.9 billion) and four times those of stroke (€5.5 billion)³². Today, approximately 820,000 people are living with dementia in the UK alone, each costing €30,622 per year, which is more than the median UK salary of €27,358. For comparison, cancer costs an average of €6,644 per patient, stroke an average of €5,283 per patient and heart disease an average of €3,827 per patient.³³

A recent Alzheimer's Disease International report "calls on governments and other major research funders to act now to increase dementia research funding ... to a level more proportionate to the economic burden of the condition. Recently published data from the UK suggests that a 15-fold increase is required to reach parity with research into heart disease and a 30-fold increase to achieve parity with cancer research."³⁴ With AD's prevalence and costs rising every year, Dr Daisy Acosta, Chair of Alzheimer's Disease International, has called it "the single most significant health and social crisis of the 21st century."³⁵

High social burden

"The care of people with dementia is not just a health [or economic] issue – it is a massive social issue,"³⁶ according to Professor Martin Prince, a psychiatrist and AD expert. Patients with AD are highly dependent on their caregivers for all their daily needs, which means their caregivers shoulder a significant burden. An institutionalised patient may merit 24.8 hours of a caregiver's time per week, but if a patient continues to live within a non-specialised care community, a caregiver will spend an average of 68.2 hours per week on the patient.³⁷ These

²⁸ [Ibid.](#), page 7.

²⁹ [Ibid.](#), page 11.

³⁰ "Report: Global cost of dementia is soaring," *Fox41.com*, 21 September 2010.

³¹ Commission of the European Communities, [Communication from the Commission to the European Parliament and the Council on a European initiative on Alzheimer's disease and other dementias](#), page 3.

³² All figures from this sentence to the end of the paragraph have been converted from British pounds sterling to euros based on end-of-year conversion rates of 1 British pound sterling = 1.4146 euros in 2004 and 1 British pound sterling = 1.1076 euros in 2009.

³³ Alzheimer's Research Trust, "[Dementia Statistics](#)," 2010.

³⁴ Anders Wimo and Martin Prince, [World Alzheimer Report: The Global Economic Impact of Dementia](#) (London: Alzheimer's Disease International, 2010), page 7.

³⁵ "Report: Global cost of dementia is soaring," *Fox41.com*.

³⁶ Christian Nordqvist, "[Dementia To Cost The World \\$601 Billion This Year, 1% Of Global GDP](#)," *Medical News Today*, 21 September 2010.

³⁷ Pfizer, "[New Research Presented at Alzheimer's Association International Conference on Alzheimer's Disease Indicates Alzheimer's Disease May Lead to Increased Comorbid Conditions and Economic Burden](#)," news release, 13 July 2010.

levels of care take their toll: for example, 40%–70% of AD patient caregivers report some psychological morbidity.³⁸ Additionally, society suffers from the loss of the caregivers' social and economic contributions, as their time and energy must largely go to caregiving. With the incidence of AD in Europe expected to increase by 40% by 2030 and by 87% by 2050, there is a critical need to decrease AD patients' dependence on their caregivers to maintain a more productive society.³⁹

The complex biology of AD and the current state of research

The biological underpinnings of AD remain poorly understood, despite agreement among scientists on certain neurological and genetic characteristics of the disease. This lack of understanding is due in part to inadequate information regarding the ageing process itself. Patients with AD display some telltale signs of ageing, particularly brain inflammation and narrowing of brain arteries. Further, scientists have noted the accumulation of beta-amyloid plaques – aggregates of protein fragments – in the brains of patients with AD. Recent data suggest that these plaques are not removed from the brain efficiently⁴⁰ and produce toxic effects on neurons and affect neural communication. Additional brain abnormalities in patients with AD include the appearance of neurofibrillary tangles, which are composed of mutant forms of a protein called *tau* and upset normal cell activity. The triggers for the formation of these brain abnormalities remain unclear. Moreover, the extent to which these protein aggregations in the brain can be prevented, slowed down or reversed in order to stop or slow the progress of the disease – or to prevent it from arising in the first place – is unknown. Recently, scientists have suggested that variants of the genes APOE and SORL1 may be risk factors for AD. While these data have provided targets for the treatment of symptoms, scientists continue to pursue an ultimate cure, with biomarkers potentially moving the world closer to a clearer solution.⁴¹

At present, there is no cure for AD. Existing treatments on the market and in research pipelines target disease symptoms rather than the course of the disease itself.⁴² AD experts suggest that the biology of the disease is so intertwined with metabolic and neurological function that “a single cure for Alzheimer’s disease is unlikely to be found,” and that successful treatment “will likely require co-ordination of a variety of treatments directed to multiple disease targets.”⁴³

Diagnostic advances

Recent progress in AD diagnostics, however, has opened a new chapter in how the medical community responds to the disease. Previously, certain diagnosis of AD could be accomplished only after autopsy, and clinicians relied on a panel of behavioural indications to evaluate a living patient’s condition. Patients with AD underwent a battery of examinations, including a mental

³⁸ Martin Prince and Jim Jackson, eds. *World Alzheimer Report 2009: Executive Summary*, page 14.

³⁹ *Ibid.*, page 8.

⁴⁰ KG Mawuenyega, W Sigurdson, V Ovod, L Munsell, T Kasten, JC Morris, KE Yarasheski and RJ Bateman, “Decreased clearance of CNS beta-amyloid in Alzheimer’s Disease,” *Science*, 9 December 2010.

⁴¹ National Institute on Aging, “Looking for the Causes of AD,” 27 October 2009.

⁴² F Mangialasche, A Solomon, B Winblad, P Mecocci and M Kivipelto, “Alzheimer’s disease: clinical trials and drug development,” *Lancet Neurology* 9, no. 7 (July 2010), pp 702–16.

⁴³ *Ibid.*, page 713.

status test, a basic physical exam, a neurological exam and brain imaging studies. After death, clinicians evaluated pathological slides of the patient's brain to confirm the presence of the anatomical markers of the disease.⁴⁴ Recent discoveries, however, may enable the diagnosis of AD prior to death, and even before symptoms emerge. In contrast with existing behavioural tests, these diagnostics rely on biomarkers characteristic of AD to identify the disease state within hours or days of a test.

Newly developed diagnostic tools include a non-invasive positron emission tomography (PET) scan to reveal amyloid plaques in the brain,⁴⁵ a blood test that evaluates 100 proteins in combination with genetic and other patient information,⁴⁶ and a spinal fluid test that identifies the presence of beta-amyloid and *tau*.⁴⁷ Clinicians can use these tests for accurate and early diagnosis, for predicting disease progression and for monitoring disease progression.

In addition to potential applications in the clinic, these new biomarkers hold promise for AD medicine research and development. They may be used, for example, to more effectively track side effects when running clinical trials of new drugs, thus supporting safer clinical trials and aiding decisions on whether to proceed to the next clinical trial stage. They also facilitate dose optimisation and the stratification of patients based on the likelihood that they will benefit from a specific treatment, thus shortening trial length, improving the response rate and potentially increasing the cost-effectiveness of a drug by avoiding treating patients who will not benefit. Biomarkers may eventually play a role as surrogate endpoints to predict a clinical outcome, or as a basis to evaluate disease-modifying claims regarding the drug.⁴⁸ Because of their many applications, biomarkers will play a significant role in efforts to improve healthcare outcomes of patients with AD.

Diagnostics: a public benefit?

Despite the conceptual link between diagnostics, biomarkers and drug development pathways, members remain split on the benefit provided by new AD diagnostics. Members noted that biomarkers and diagnostics are of significant importance in other disease areas (e.g., cancer) as well. Indeed, pre-meeting comments regarding the benefit from an AD diagnostic quickly evolved into a broader discussion on the link between diagnostics, biomarkers and drug development more generally.

One member stated that he *“did not understand what the benefits are of a diagnostic when there is no effective therapy for the underlying condition.”* Similarly, another expressed *“substantial reservations about the taxpayer paying for that diagnosis in circumstances where the provision of that information does not, as yet, have any public benefit.”*

⁴⁴ Alzheimer's Association, [“Steps to Diagnosis,”](#) 17 November 2010.

⁴⁵ H Hampel et al., “Biomarkers for Alzheimer's Disease: Academic, Industry and Regulatory Perspectives,” *Nature Reviews: Drug Discovery* 9, (July 2010), pp 560–74.

⁴⁶ Julie Steenhuisen, [“Simple Blood Test May Detect Alzheimer's: Study,”](#) *Reuters*, 13 September 2010.

⁴⁷ Gina Kolata, [“In Spinal-Fluid Test, an Early Warning on Alzheimer's,”](#) *New York Times*, 9 August 2010.

⁴⁸ Hampel et al., “Biomarkers for Alzheimer's Disease.”

However, other members emphasised the ways in which biomarkers that are the basis of new diagnostics could be of benefit in the development and testing of new drugs. One member stated, *“The new diagnostics have identified biomarkers that signal very early in disease progression who will later develop Alzheimer’s ... These biomarkers are helpful for pharmaceutical companies that develop medicines, as they also suggest pathways for the medicines to impact. The biomarker will also assist regulators in determining Alzheimer’s medicine efficacy and safety.”* Another member stated that *“Alzheimer’s is an example of the need to have diagnostics and biomarkers for the inclusion and exclusion of patients from clinical trials and eventual treatment. Only by doing this will we increase response rates by stratifying patient populations.”* This member suggested that such stratification could *“lead to greater cost-effectiveness of medicines that are being used, as it will eliminate the problem we have today when 70–80% of a patient population often receives no benefit from a new drug.”* By targeting treatment towards patients that are expected to benefit from a specific medicine, patients that are likely to fail to respond to a treatment can be proactively identified, lowering aggregate healthcare costs and limiting exposure to drugs that may cause dangerous side effects. Thus, while diagnostics may not provide a short-term therapeutic benefit without a concurrent therapy in place, they may spur drug development over the long term. One member observed that the potential for health systems to refuse to pay for diagnostics because of the (current) lack of direct health benefit *“does not take into account the long-term benefit [that] the diagnostic and biomarker have on drug development.”*

Ethical considerations surrounding testing when there is no cure

In addition to the issue of balancing a potential long-term benefit with a certain short-term cost, there are also ethical issues involved in administering a diagnostic for a disease with no known effective therapy. One member suggested that while an individual citizen might want to take an AD diagnostic test for personal reasons, such as preparing for a family’s future, *“we need to be very careful about whether this is something that the national system should reimburse for.”* One member believed that the reason for taking the test should be an important basis for the state’s role in reimbursing for the diagnostic, as he *“would want to be sure a patient was taking the test for the right reason and had the right support around them before providing a subsidy to determine if an awful death from Alzheimer’s is a likely future.”* Another member suggested that a protocol including careful professional counselling – similar to the Huntington’s protocol⁴⁹ – should be a necessary accompaniment to any AD diagnostic test.

⁴⁹ In 1989, a committee comprising members of the International Huntington Association and the World Federation of Neurology drew up a protocol for testing presymptomatic people for Huntington’s disease, an incurable neurological disease. See David Craufurd and Audrey Taylor, [“Predictive Testing for Huntington’s Disease: Protocol of the UK Huntington’s Prediction Consortium.”](#) *Journal of Medical Genetics* 29, no. 12 (December 1992), pp 915–18.