

Meeting summary

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
TYPE 2 DIABETES WORKING GROUP

14 OCTOBER 2009

The Agenda for Change: Improving Health Outcomes in Type 2 Diabetes

Overview

Initiated by the European Healthcare Innovation Leadership Network, the Type 2 Diabetes Working Group brings together world-class thought leaders and decision-makers from the ranks of medical experts, regulators, HTA, payers and advisers, patient representatives and industry. Working together over the course of 2009, Working Group participants are committed to addressing unmet needs in type 2 diabetes by establishing a shared value framework for drug development in this area and developing approaches to overcome barriers to innovation through more effective collaboration among all stakeholders.

A shared value framework is a recommended approach arising from collaboration among key stakeholders to encourage changes in how the value of new medicines can be assessed, demonstrated, captured and rewarded with the end goal of improving health outcomes. This could range from an aligned perspective on the basic science and epidemiological information underlying a given disease, to new approaches supporting a comprehensive view of drug development, or an agreed code of conduct among stakeholders to facilitate these new, more collaborative behaviours.

To move towards the tangible outcome of a shared value framework, the Working Group is creating a “21st century” type 2 diabetes drug development template. The goal of the template is to provide an improved process for drug development that refocuses stakeholders on shared definitions of value and accelerates patient access to innovative medicines.

The Working Group held its second meeting in London on 24 September 2009 to develop the components of the “21st century” type 2 diabetes drug development template and identify potential pilots to test such a template. It was preceded by multiple rounds of discussion with participants to set the agenda and capture the views of those unable to attend. The session comprised a mixture of plenary discussion, focused work in breakout groups, and individual consideration to obtain perspectives on emerging issues. A modified version of the Chatham House Rule was used throughout the day, whereby names of participants and their affiliations are a matter of public record, but comments made during meetings are not attributed to individuals or organisations. This document summarises that day’s discussion and sets the roadmap for the next Working Group meeting on 8 December 2009.

Table 1 contains the membership of the Working Group by stakeholder group, with those in attendance shown in black.

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Participants

Medical subject matter experts

- **Amanda Adler**, Institute of Metabolic Science, Cambridge, UK
- **Jean-François Bergmann**, Hôpital Lariboisière Paris, France
- Christian Berne, Uppsala University, Sweden
- John Buse, University of North Carolina, USA
- Bernard Charbonnel, University of Nantes, France
- Ele Ferrannini, University of Pisa School of Medicine, Italy
- Vivian Fonseca, Tulane University Medical Center, USA
- **Philip Home**, Newcastle University, UK
- **Harald Klein**, Ruhr-Universität Bochum, Germany
- **Mohan Kumar**, NHS North Western Deanery, UK
- Andrew Morris, University of Dundee, UK
- **Eberhard Standl**, Munich Diabetes Research Institute, Germany

Payers, regulators, health economists and advisors

- Eric Abadie, Committee for Medicinal Products for Human Use (CHMP), Europe
- **Andrew Briggs**, University of Glasgow, UK
- Hans-Georg Eichler, European Medicines Agency (EMA)
- **Peter Kolominsky-Rabas**, University of Erlangen-Nuremberg, Germany
- **Félix Lobo-Aleu**, Universidad Carlos III, Spain
- Noël Renaudin, Economic Committee for Health Products (CEPS), France
- **Michael Schlander**, Institute for Innovation & Valuation in Health Care, Germany
- Angelika Szalayová, Health Policy Institute, Slovak Republic
- Sjaak Verduijn, CZ Insurance, The Netherlands

Patient representatives

- **Maarten Ploeg**, Dutch Diabetes Association, The Netherlands

Industry representatives

- **Martin Fitchet**, Johnson & Johnson
- **Gunnar Olsson**, AstraZeneca
- **Carlo Russo**, GlaxoSmithKline

Executive summary

Building on a consensus framework of value indicators and measures developed over the course of the year, the second meeting of the Type 2 Diabetes Working Group identified opportunities for enhanced collaboration among stakeholders and highlighted the need for such collaboration to support the continued development of innovative medicines. As discussed in greater depth later in this document, the following were the meeting's principal outcomes:

- **Assessing value in type 2 diabetes medicines** (*page 4*). Tapestry Networks reported to the Working Group a consensus set of value indicators and measures developed and refined with the Group's input. This framework is the first component of the 21st century drug development template. Participants applied the framework to three simulated medicine profiles.
 - The Working Group validated the set of indicators and measures as appropriate for value assessment in type 2 diabetes medicines.
 - The discussion showed that even an agreed-upon set of such indicators cannot by itself remove the ambiguity inherent in drug development, particularly as it pertains to innovative medicines.
 - Reducing risk and ambiguity requires the engagement of payers and, to a lesser extent, regulators around the value framework as applied to classes of or individual medicines.
- **Enhancing stakeholder interactions** (*page 6*). The Working Group highlighted the importance of expanded consultation among stakeholders and identified behaviours that stakeholders should *start* and *stop*. Participant calls for “*transparency and openness of [the drug development] process,*” along with early consultation among stakeholders, appear to hold the greatest promise for significant progress in the development of type 2 diabetes medicines.
 - Participants noted that diabetes is one of the most expensive therapeutic areas for drug development and called for enhanced interactions to help guide and justify industry investment decisions.
 - Lack of transparency and the absence of consultation also create a disproportionate barrier to innovative medicines, whose development is inherently more risky than that of those with an established mechanism of action. In these cutting-edge areas of science, stakeholders suggest that industry needs to share information to provide the basis for a common understanding with regulators and payers. This common understanding can then serve as the basis for constructive dialogue.
 - Participants identified Phase II of the drug development process as the most valuable time for consultation. They cited the most pressing topics for discussion and

agreement during these Phase II interactions as: (1) the medicine's target profile and evaluation criteria for reimbursement; (2) its potential indications; (3) its positioning in the treatment hierarchy; (4) the therapeutic endpoints of concern and ways to demonstrate value; and (5) the medicine's safety and side effects.

- Although most participants consider Phase II as the appropriate time to engage in consultations, the meeting also surfaced a proposal for an additional consortium approach by which several companies meet jointly with reimbursement authorities to discuss more generalisable issues in drug development not necessarily tied to a specific pipeline asset.
- In considering broadly the behaviours that stakeholders should *stop* and *start*, the resounding message was the desire of all participants for enhanced transparency and collaboration throughout the drug development process.
- **Considering reimbursement on the basis of health outcomes** (*page 13*). Participants see a potential future role for healthcare integrators who are reimbursed on the basis of disease management and health outcomes (rather than, *i.e.*, the doses of medicine prescribed). Some participants are uncomfortable with pharmaceutical companies taking on this role for fear they may give undue preference to their own products in managing health outcomes. However, others believe such companies may be well-placed to do the job if constraints on potential bias and measures to ensure cost-effectiveness can be put in place.
- **The road ahead** (*page 15*). Building on the enthusiasm and tangible progress generated by discussion of the simulated medicine profiles, the Working Group will work toward a set of pilots to round out and apply the 21st century drug development template.

Assessing value in type 2 diabetes medicines

Advancing the 21st century drug development template

Participants at the Working Group's first meeting on 20 May considered and discussed the most pressing unmet medical needs in type 2 diabetes; barriers to progress in better addressing those needs; and potential solutions for overcoming those barriers. The recommended solutions offer a slate of activities that participants believe can improve both the process and products of drug development. Rather than taking up these initiatives in a piecemeal approach, Tapestry Networks has suggested that they form integral elements of what might be termed a "21st century drug development template for type 2 diabetes" that can be deployed along the drug development lifecycle. The template consists of three major components:

- A tiered set of value indicators and measures required to demonstrate benefit in addressing unmet needs along the drug development life cycle

- A process for early consultation with regulators, HTA and payers
- Principles and criteria for use of post-launch mechanisms to encourage innovation and value-based pricing

The Working Group has advanced the drug development template by agreeing the first of these components. Tapestry Networks has refined this set of indicators and measures for the assessment of value in type 2 diabetes medicines, to help overcome what one participant termed “*a tower of Babel*” problem in which stakeholders speak about value without each of them knowing what is meant by another. Following many rounds of revision based on Working Group participant comments, these indicators and measures can serve as a comprehensive, consensus framework that contains the characteristics of a medicine that are relevant to assessing its therapeutic value in the treatment of type 2 diabetes. This framework is included as Appendix 1.

To be clear, we do not suggest that a given drug should demonstrate performance along *every* value component included in the framework. Rather, the framework is intended as a menu of indicators and measures from which stakeholders can select the relevant value demonstrations to satisfy the requirements of a given regulatory or reimbursement dossier.

Pre-meeting discussions yielded a number of comments regarding the framework’s application. As a starting point, several participants stated that differentiation from the standard of care, not merely efficacy, is the reliable path to reimbursement. An HTA-payer participant explained: “*It is not enough to get evidence that the medicine is working, but that it is different from medicines that are already reimbursed.*” The two cornerstones of existing therapy are metformin and insulin. One offers an inexpensive and relatively well-tolerated treatment, while the other delivers unsurpassed glucose lowering. In the face of these comparators, new medicines are well-served to show distinction in areas such as durability of control, an improved adverse effects profile, effectiveness in patients who are failing on other therapies, and the capability to replace combination therapies.

Applying the framework

The Working Group considered three medicine profiles that were described by a set of indicators and measures drawn from the above framework. Tapestry Networks developed these realistic but simulated profiles with the active involvement of participants to stimulate discussion. The profiles described the following medicines:

- A medicine with an early indication of cardiovascular benefit and a moderate (0.5%) HbA1c reduction
- A biological with the potential of arresting disease progression
- A medicine producing a large (1.4%) HbA1c reduction coupled with a significant weight gain

Appendix 2 summarises the discussion of the three profiles. The exercise was instructive in several respects:

- First, the Working Group validated the set of value indicators and measures as an appropriate framework for describing the value of a medicine for type 2 diabetes. The discussion did not identify any additional indicators of value that should be added.
- Second, the discussion demonstrated that even a consensus view of indicators and measures for describing the value of a medicine fails to resolve all of the ambiguity inherent to drug development. In particular, the lack of regulatory and reimbursement precedent for innovative medicines leads to a more uncertain and difficult development path when compared to drugs that build upon or duplicate a well understood mechanism of action.
- As a consequence of the second point, the Group strongly supports additional early consultation with payers (and to a lesser extent regulators) in order to create a receptive environment for innovative medicines – without which several promising drugs simply would not be developed. The Group assumed that the discussion would take place during Phase II, sufficiently early for industry to share information with and seek counsel from other stakeholders while still having actual trial results to anchor a discussion of Phase III trial design and value demonstration.

The foregoing discussion underscores the importance of early stakeholder consultations, particularly as they may enhance the development of truly innovative medicines. The meeting represents significant progress for the Working Group in defining not only the need for these interactions, but in starting to give form and substance to them.

Enhancing stakeholder interactions

Implementing a process of enhanced interactions among stakeholders is the second component of the 21st century drug development template. Leading up to and during the meeting, participants identified opportunities for relevant stakeholders to share information and provide early guidance for approval and reimbursement in the drug development process, as well as behaviours that stakeholders should *start* and *stop*. As discussed below, expanded consultations are needed not only to guide industry's investment and prioritisation decisions, but also to create a transparent and receptive environment for the development of truly innovative medicines. Hence, early consultation among stakeholders appears to hold the greatest promise for significant progress in the development of type 2 diabetes medicines.

The need for early stakeholder interactions

Participants have described the goals of enhancing early and on-going stakeholder interactions as “*very important*” and “*the main point of all of the Working Group’s deliberations.*” Further comments suggest that the insight sought by various stakeholders can only be achieved through a collaborative process. Speaking for one group of HTA-payers, a participant stated that, “*because*

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diabetes is a complex disease, it is necessary for all stakeholders to work together in order to achieve superior outcomes to each of us working in a more fragmented way.” He called for “*closer cooperation*” between regulators, reimbursement authorities and industry, defined by “*transparency and an openness of process.*” Payers, in particular, “*should be explicit and transparent about their decision making.*”

Participants are particularly interested in achieving a better understanding of reimbursement criteria. As an HTA-payer acknowledged, “*payers need to send very clear messages to industry about what sort of evidence they want to see. And a part of that will involve early consultation and clear guidelines for what needs to be accomplished after market access.*” Another HTA-payer explained that “*when you have contacts a few years before the drug gets to regulatory approval, the HTA authority can describe what information will be needed for reimbursement, and point out if that is missing from the existing trials.*”

This is exactly the type of consultation industry and other stakeholders are seeking. Speaking for his breakout group of industry representatives, a participant explained the dichotomy the pharmaceutical industry faces: “*we have clear regulatory guidance. What we do not have a clear input on is what justifies value or price or reimbursement for a medicine.*” Yet, “*[licensing] approval is obviously just the beginning and does not justify the development cost of the product.*” Other participants also acknowledged that such transparency is missing from the current process. A medical expert lamented that “*the problem in Europe is that industry has tried [to achieve greater clarity], but there is nobody to meet them to provide that advice.*”

The discussion highlighted two related objectives for which early consultation, particularly with HTA and payers, is critical:

- To guide and justify industry’s drug development investment decision
- To create a receptive environment for truly innovative medicines

We address each of these below.

Guiding and justifying investment

Diabetes drug development entails “*very massive investments.*” In particular, “*a diabetes drug now costs about \$500 million to \$600 million to develop.*” As a result, “*diabetes drug development is now up there with atherosclerosis as the most expensive development programmes in industry.*” The sheer size of these investments, coupled with the perceived lack of transparency as to the criteria for reimbursement, creates a level of risk relative to other therapeutic areas that makes developing drugs for type 2 diabetes difficult to justify for industry participants. This difficulty is particularly acute with respect to biologicals, for which “*most of the decisions that need to be made for a pharmaceutical product are going to be made earlier and at greater risk.*”

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Indeed, the costs and risks of diabetes drug development create pressures within industry to prioritise other areas. As an industry participant explained, *“we can develop three drugs in virology for the price of a drug in diabetes which actually could generate three times as much income if you are looking at Hepatitis C or drug resistant HIV.”* He continued:

Without wanting to blind people with all this talk of large sums of money, the point is that it is all about choices in pharma companies just like it is with people who are reimbursing medicines across therapeutic areas. We need all the help we can get as early as possible to persuade our boards and our shareholders to make those choices [in favour of diabetes].

Industry’s preferred solution to this dilemma is *“more and much earlier interaction with other stakeholders about what is needed to demonstrate the value of a new medicine.”* Such input would provide *“a much better understanding as to whether the investment is justifiable.”*

In seeking this input, industry participants were quick to point out that the issue is risk, not cost. One industry participant explained that *“from my point of view, the cost is not the issue; it is the risk. I would rather spend more money with a better probability of success than spend less money with a much higher risk.”* A counterpart from another company continued: *“The development decisions are entirely our responsibility to take and our risk as pharma companies. We are not looking for anybody to take that risk; we are simply looking for a more transparent discussion earlier on that would help us to understand it.”* Such transparency would help *“with the decision-making specifically to say “no” to things that you do not want to progress to Phase III,”* as well as provide guideposts as to what ultimately will be reimbursable. As noted in the previous section, HTA-payer participants are generally in agreement with the importance of *“sending very clear message[s] to industry”* to *“describe what information will be needed for reimbursement.”*

Creating a receptive environment for innovative medicines

The lack of transparency and consultation creates significant obstacles for the development of innovative medicines. Yet, given the substantial unmet medical needs in type 2 diabetes identified in the Working Group’s first meeting, it is just such medicines whose development stakeholders would encourage. In the opinion of a medical expert, an important barrier to effective engagement *“is that payers actually don’t know how the scientific landscape is evolving over the next three to five years time because these are rapidly changing areas. As a consequence, industry can’t get a clear view from payers not because they are being willfully obstructive but because payers themselves don’t know.”*

Participants believe that early interactions are needed to create the common understanding of disease processes and therapeutic approaches necessary for HTA and payers to engage industry around innovative medicines. They cited a need *“to create a better mechanism for payers and regulators to understand the metabolic arena going forward and to actively engage in that dialogue.”* Such a mechanism would rest on *“a non-threatening and balanced way to*

communicate.” As an industry participant concluded, “the great value in this engagement is the mutual understanding of what a product under development actually is and what it can accomplish.”

This need is particularly acute with respect to the most innovative medicines. A medical expert lamented: *“If I look at some of the newer products that are coming along ... my experience is that because [payers and regulators] have not seen them before they do not begin [to engage]. Their thinking is virtually at zero.”* An industry participant highlighted the difficulties caused by the late engagement of reimbursement authorities:

The advantage the regulatory agency has over the payers and HTA is they are with us through the journey and therefore whenever we present something it is not taken out of context ... The problem with payers and HTA is that if we come with a final package they have no clue how we got there. The only thing they can do is compare to Metformin. I have to communicate in a small period of time things that took five, six, seven years to go through.

And while several participants praised the consultative mechanisms available with regulatory agencies, a medical expert suggested that even their openness to innovation is limited by *“an outdated perspective on the state of the art that has been determined by the way diabetes drugs were developed in the past.”* He characterised the challenge as *“finding a way to get a more current view in place.”*

The content of early stakeholder interactions

Beyond agreeing the need for early stakeholder consultations, participants discussed the topics that such consultations should address. Given the acknowledgment that reimbursement authorities do not have readily available answers to all of industry’s questions, it is most helpful to approach these interactions as a mechanism for creating the exchange of information and depth of understanding necessary for informed and constructive collaboration. With this caveat in mind, participants identified the following aspects of a drug development program that should be discussed and agreed as part of early interactions, most likely during Phase II:

- The medicine’s target profile and evaluation criteria
- The medicine’s potential indications
- The medicine’s positioning in the treatment hierarchy
- Therapeutic endpoints of interest and ways to demonstrate value
- The medicine’s safety and side effects

We address each of these topics below.

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Target profile and evaluation criteria

Industry's primary concern is to achieve a level of clarity on how reimbursement authorities will assess the value of new medicines. While the framework of indicators and measures forms a sound basis for this, discussion of the three medicine profiles illustrated that collaborative engagement focused upon specific assets is required for many – if not most – drugs under development.

As a starting point, industry approaches drug development with a target product profile. Participants sought a mechanism for stakeholder participation in a discussion – and validation – of whether *“we have the right profile for what we believe is a good drug.”* This feedback is particularly relevant early in the development process when limited data has been generated about a drug, to provide a view of whether industry's target profile – if it is achieved in practice – would be reimbursable.

This discussion translates to *“what is the probability for us in Phase III to demonstrate what you believe is a good drug?”* Industry representatives were quick to point out, however, that they are not seeking a prediction as to reimbursement price. Rather, they *“are asking what criteria [the reimbursement authority] is going to use to define whether or not it is willing to pay for the product.”*

Potential indications

The Working Group's discussion of simulated drug profiles illustrated that it may be challenging to determine the appropriate indication for a new medicine, particularly one with an innovative profile or one demonstrating effects along multiple endpoints. Consensus on the appropriate indication to target would be a critical benefit of early interactions, because it would determine the course of the development plan for the medicine, as well as the size and nature of its potential market. An important element of this discussion is whether there are particular subgroups for which the drug is particularly effective, or, in the alternative, contra-indicated.

Positioning in the treatment hierarchy and appropriate comparators

Closely related to a medicine's indication is its position along the chain of diabetes treatment options, leading to a determination of where a new medicine is to be used relative to existing drugs. As a medical expert explained, *“a new glucose lowering drug goes into a pathway which has a series of drugs and it could be compared to any of them.”* The question of to which existing drug a new medicine is compared – that is, what is its comparator in terms of cost and effectiveness – is critical to value assessment, and an important topic for early consultation.

The choice of comparator, in turn, affects the development plan by specifying the medicines or medicine combinations that need to be tested in clinical trials alongside the asset under development. For a first-line indication, the comparator is metformin unless the medicine is targeted specifically toward patients who are metformin intolerant. For a second-line indication

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as an add-on to metformin, a reimbursement authority may “ask for trial versus placebo or versus another second line drug such as a DPP-4.”

Endpoints of interest and ways to demonstrate value

The Working Group’s discussion of simulated medicine profiles demonstrates the importance of early consultation to identify endpoints of interest and study design, particularly for innovative medicines. Here participants considered medicines that promise significant long-term value beyond launch, and asked, “*how could I have the confidence to invest in*” the long-term data development program needed to demonstrate this value? As an industry participant concluded with regard to one of the simulated medicines profiles, “*the only way you would develop this medicine is if you could get good input from regulators and payers pre-Phase III.*” Thus, the importance of early consultation regarding endpoints and ways to demonstrate value along them is that, without some early assurance from reimbursement authorities as to the appropriateness of the data development plan, industry may not invest in, and patients and health systems may miss out on, a medicine that could deliver significant long-term benefit.

Safety and side effects

Multiple HTA-payer participants have stated that a drug’s mechanism of action “*is not a factor for reimbursement or pricing but it is important for explaining the potential side effects ... [because] it is necessary to explain how [the medicine] works.*” This is an area of increasing importance – and increasing cost – as a medical expert remarked that “*today, from the regulatory point of view, safety is more important than efficacy.*” An industry participant explained that, as a result, “*the problem of study cost to get a drug to market has become particularly acute in the United States, where the FDA has introduced guidance on the need to do large pre- and post-approval cardiovascular studies.*” Similar requirements may follow in Europe. A fellow participant added that “*the challenge right now is finding the balance of value between more safety assessments without making the cost of drug development untenable.*”

With the ever-increasing attention being paid by regulators and payers to drug safety, early consultation as to a drug’s mechanism of action can orient the developer’s testing plan as to demonstrating safety or – just as importantly – provide an early signal to terminate development due to safety concerns.

The timing of early stakeholder interactions

Alongside the content, the Working Group focused their attention on the timing and circumstances of enhanced stakeholder interactions. This discussion included three concepts:

- **Meet during Phase II.** Throughout the working group process, the emphasis has been on expanding interactions in and around Phase II, and this focus was maintained at the 24 September meeting. As noted above, HTA-payer participants expressed support for “*contacts [with industry] a few years before a drug gets to regulatory approval.*” An industry representative summed up this approach, stating that “*there is a need around*

Phase II to bring in the payers. Right now ... there is no mechanism in place to engage the different payers for this type of discussion.” The content and context of these interactions was discussed in detail earlier in this section.

- **Meet after Phase III at the time of NDA filing.** Another industry participant suggested an alternative approach, focusing instead on meeting with reimbursement authorities toward the end of Phase III, *“before the regulatory review but when you have Phase III data.”* The advantage of this approach is that it allows more effective coordination in a more data rich environment, while *“still giving [industry] a year to re-analyse or generate new data or start new studies to meet value endpoints based on feedback.”* This meeting would then be followed by another one once the medicine has obtained regulatory approval (which is currently when the first set of meetings with reimbursement authorities typically take place). Relative to meeting in Phase II, this approach has the advantage of a discussion more firmly grounded in clinical trial data, but carries the disadvantage of providing payer insight later along the drug development path and possibly adding new evidence requirements after Phase III.
- **Meet as a consortium.** As a complement to the above two approaches, a suggestion presented at the 24 September meeting would have several companies meet jointly with reimbursement authorities to discuss more generalisable issues in drug development *“across the board and not necessarily on a case-specific basis.”* This suggestion follows from the Group’s experience in discussing simulated drug profiles and would focus on *“a class of product or a profile that we think is reasonable.”* The advantage of such an approach is that it would more closely approximate a *“non-threatening and balanced”* environment that participants have called for, while providing potentially a more efficient use of limited HTA-payer resources. It may be a particularly appropriate venue for seeking consensus on disease models as well as the exchange of information about particular mechanisms of action.

The discussion of these approaches on 24 September represents significant progress not just in building an appreciation of multiple stakeholder perspectives, but also in beginning to define new ways of collaboration to improve the efficiency and effectiveness of drug development. Further to this objective, the Group identified particular stakeholder behaviours that are beneficial as well as those that represent barriers to progress.

Changing behaviours of key stakeholders

There was widespread agreement that stakeholder behaviours need to change in order to enable a new approach to drug development and improve patient access to innovative medicines. During one breakout session, participants grouped by stakeholders detailed behaviours that stakeholder groups should *stop* and *start*.

The similarity of stakeholder views as to desirable behaviours lead one HTA-payer participant to conclude that *“my one key takeaway from this meeting is just how much common ground we*

have.” Indeed, the themes that emerged from this discussion reinforce those running through this document. The resounding message was the desire of all participants for enhanced transparency and collaboration throughout the drug development process. Other key areas of need include:

- early engagement of all stakeholders in the drug development process
- comprehensive approach to diabetes care
- increased adherence among clinicians to evidence-based treatment guidelines
- harmonisation of requirements between regulators and payers, and among payers in the various Member States

We include in Appendix 3 a full summary of stakeholder behaviours to *stop* and *start*.

Considering reimbursement on the basis of health outcomes

The meeting included a discussion of recent trends toward an approach to reimbursement that reinforces the holistic management of type 2 diabetes. There is an emerging interest among health systems in a movement from the reimbursement of isolated health interventions to payment contingent on achieved health outcomes. This trend in part recognises the complementary and synergistic roles played by medicines, medical devices and education programs in treating type 2 diabetes, as well as the central position of the patient in many successful long-term disease management strategies.

In pre-meeting discussions, participants focused their attention on four non-medicinal factors that have a significant impact on type 2 diabetes health outcomes:

- The organisation of the delivery of care
- Improving nutrition and lifestyle
- Timely and effective provision of information to patients
- Enhancing compliance with treatment regimens

At the meeting, participants quickly dispensed with improving nutrition and lifestyle as a viable stand-alone strategy for driving health outcomes. They noted that lifestyle interventions come too late, because *“you cannot heal the disease [once it starts] by changing lifestyle;”* or have little lasting effect, as *“you start with a very enthusiastic patient group ... but after six weeks, the adherence goes down tremendously.”*

Thereafter, participants focused their discussion on the potential of an integrated approach to healthcare services to improve health outcomes, in part through its effect on the factors listed above, and in part through the inclusion of medical interventions additional to medicines. At an

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individual level, participants identified *“a need for a para-medical person assisting primary care doctors or any system on a public health level”* or, alternatively, *“an integrator who works with individual population sub-groups or specific individuals.”*

At a programmatic level, participants considered the experience with pharmaceutical companies providing nurses to health systems to act as case managers of diabetic patients, as well as other disease areas where industry has sponsored *“para-medical”* personnel to provide information and training. The discussion centred on the tension between improved health outcomes that result from such interventions, and interference in the healthcare system by a company that is likely to be biased in favour of its own products.

On the positive side, participants were of the opinion that *“you may actually accept some bias to get the advantage”* of improved health outcomes. A medical expert recounted his experience with a nurse who was expert in managing pulmonary disease, sponsored by a company that manufactures inhalers. He acknowledged that *“there was a conflicting agenda”* but concluded that *“the benefits are significant in terms of the case management and the education provided to the nurses, which is freeing up the practitioners to manage these cases.”* The result – *“a significant reduction in hospital admissions”* – has led to overall cost savings that make the intervention worthwhile from a health system perspective. Moreover, according to another medical expert, such a profit motive *“may be the only way [disease management] actually gets done.”*

Positive experiences notwithstanding, the notion of disease management interventions undertaken by pharmaceutical companies was uncomfortable for several participants. A medical expert stated that *“it is hard to imagine that [the intervention] would mainly be educational. One would assume there is a profit motive.”* A fellow medical expert added that *“it has to be an independent institution, without any hint of conflicts or bias.”* For this reason, an HTA-payer participant concluded that *“it should be the health systems that are taking the initiative, not the pharmaceutical industry.”*

Despite these misgivings, industry is considering its role in a possible future system that provides reimbursement directly for disease management. An industry participant saw an *“opportunity for companies that have a significant amount of experience and expertise to put together”* an integrated set of disease management services. These services could include *“diet and exercise interventions, potentially bariatric interventions, and medicinal interventions ... without taking away the decision-making process from the physician or the nurse.”* He saw a need for a company interested in this field to sponsor a data development program by which payers can evaluate whether disease management is valuable or not.

An HTA-payer summed up the discussion: *“The general model of the disease management process, particularly in an area like diabetes or respiratory disease, is a very promising one.”* That said, *“the disease management programmes must be evaluated and shown to be cost effective.”*

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The road ahead

Building on a consensus framework of value indicators and measures developed over the course of the year, the Type 2 Diabetes Working group focused its discussion on applying the framework and mapping a set of enhanced stakeholder interactions. The enthusiasm and richness of dialogue generated by a set of simulated medicine profiles led several participants to call for pilots to extend the discussion to other diabetes medicines and involving other stakeholders.

Moving forward along the lines participants suggested, Tapestry Networks will propose a “rapid pilot” that will engage the Group’s expertise using a simulated medicine with a more refined profile than those employed in this meeting (to include some key guidelines, epidemiological models and pricing references). The objective will be to continue to advance and refine the 21st century drug development template. These activities will lay the groundwork for engaging a broader set of stakeholders in 2010 to apply the template to a set of actual medicines under development, thereby serving as pilots for its broader application.

In the days ahead, Tapestry Networks will be reaching out to participants to seek their insight as we develop this set of pilots and move forward in completing the 21st century drug development template for type 2 diabetes. As we close this chapter of the Working Group’s efforts, we thank our participants for their commitment to progress in this area and look forward to their continued insight and energy.

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Appendix 1: Framework of indicators and measures for assessing value in type 2 diabetes medicines

Value component	Measure
Maintaining glucose metabolism	
Glycaemic control (surrogate endpoint)	
Glycaemic control	<ul style="list-style-type: none"> ▪ HbA1c reduction (Δ %) ▪ % change in HbA1c level relative to baseline (%)
Durability of control	<ul style="list-style-type: none"> ▪ Progression of HbA1c over time (while on particular medication) ▪ Coefficient of treatment failure ▪ Time to treatment intensification
Preservation of glucose metabolism	<ul style="list-style-type: none"> ▪ Measures of improved beta cell function and / or reduced insulin resistance to be developed (e.g. c-peptide)
Avoidance of microvascular complications (intermediate and hard endpoints)	
Reduced diabetic retinopathy	<ul style="list-style-type: none"> ▪ % of patients with microvascular eye problems ▪ Time to progression of retinopathy
Reduced diabetic nephropathy	<ul style="list-style-type: none"> ▪ % of patients with microalbuminuria / proteinuria ▪ Time of progression to microalbuminuria / proteinuria ▪ Improvement of creatinine
Reduced diabetic neuropathy	<ul style="list-style-type: none"> ▪ Measures of peripheral / autonomic / proximal / focal neuropathy
Preventing cardiovascular complications	
Control of cardiovascular risk factors (surrogate endpoints)	
Weight control	<ul style="list-style-type: none"> ▪ Change relative to ideal body weight (%) ▪ Absolute change in body weight (kg) ▪ Waist circumference / change in
Reduced diabetic dyslipidaemia (improved lipids)	<ul style="list-style-type: none"> ▪ Change in LDL cholesterol level (mg/dL) ▪ Change in blood triglyceride level (mg/dL) ▪ Change in HDL cholesterol level (mg/dL)
Reduced hypertension	<ul style="list-style-type: none"> ▪ Change in systolic blood pressure (mm Hg) ▪ Change in diastolic blood pressure (mm Hg)

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Value component	Measure
Avoidance of cardiovascular disease (hard endpoints)	
Reduced cardiovascular disease morbidity	<ul style="list-style-type: none"> Age-adjusted non-fatal myocardial infarctions per patient year Age-adjusted rate of strokes per patient per year Age-adjusted urgent coronary revascularisations per patient per year
Reduced cardiovascular disease mortality	<ul style="list-style-type: none"> Annualised age-adjusted death rate due to cardiovascular events (MI, stroke, acute coronary syndrome)
Reduced all-cause mortality	<ul style="list-style-type: none"> Annualised age-adjusted death rate from all causes
Enhanced treatment safety, convenience and alternatives	
Drug safety and side effects	
Avoidance of hypoglycaemia	<ul style="list-style-type: none"> Major / minor hypoglycaemic episodes per patient per year
Avoidance of weight gain	<ul style="list-style-type: none"> Absolute increase in body weight (kg) Increase relative to ideal body weight (kg)
Improved tolerability	<ul style="list-style-type: none"> % discontinuing medicine due to side effects % reporting moderate to severe side effects
Cardiovascular safety	<ul style="list-style-type: none"> CV mortality, myocardial infarction and stroke in phase 2 and 3 trials versus comparator
Reduced serious, chronic or irreversible side effects	<ul style="list-style-type: none"> Incidence of adverse effects
Enhanced treatment convenience	
Delayed need for multiple therapies	<ul style="list-style-type: none"> Time to progression from monotherapy
Delayed or avoided need for injections (insulin or other drugs)	<ul style="list-style-type: none"> Time to progression or other injected therapies
Ease of comfort of administration	<ul style="list-style-type: none"> Degree of patient compliance with treatment regimen
Enhanced treatment alternatives	
Improved treatment alternatives for hard-to-treat subgroups	<ul style="list-style-type: none"> Subgroup-specific efficacy and tolerability
New mechanisms of action	<ul style="list-style-type: none"> First or among first medications with new mechanism of action

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Value component	Measure
Health system benefits	
Reduced demand for healthcare resources	
Reduced overall health system costs	<ul style="list-style-type: none">▪ Total expenditure per patient per year▪ Medicines expenditure per patient per year
Fewer surgical procedures required	<ul style="list-style-type: none">▪ DM-related surgical procedures per patient per year▪ Same on inpatient / outpatient basis
Reduced hospitalisation costs	<ul style="list-style-type: none">▪ Number of hospital admissions for DM and complications per patient per year▪ DM-related inpatient days per patient per year
Fewer visits to related specialities (chiropractist, nephrologist)	<ul style="list-style-type: none">▪ Specialist visits per patient per year▪ Ratio of visits to general practitioners versus specialists

Appendix 2: Discussion of simulated drug profiles

Medicine profile “A”: Early indication of cardiovascular benefit with a moderate HbA1c reduction

This was a medicine profile with a small impact on HbA1c and improvements across cardiovascular risk factors. It was characterised by the following value indicators and measures:

- An expected HbA1c reduction of 0.5%
- An expected change in body weight of -2kgs
- An expected reduction in hypertension of -5mmHg blood pressure
- A marker of reduced inflammation (C-reactive protein reduction of 15%)
- Expected pricing of medicine A was a 15x multiple relative to metformin

Medicine A presented a developmental asset that could provide benefits in micro- and macrovascular outcomes, but because of its low effect on HbA1c, may not be granted an indication as a traditional anti-diabetes drug. Thus, despite its benefits, it is likely that it would not be developed without expanded early stakeholder interactions with regulators and payers to define its target patient population and development program.

Participants noted that the low level of glucose lowering provided by this medicine would create a challenge in defining the appropriate indication at launch. They suggested that an HbA1c lowering of about 0.8% is a lower increment of value for an indication as an anti-diabetic. Adding to scepticism was the question of whether the HbA1c decline was attributable primarily to the loss of weight (in which case *“the drug is not a diabetes drug”*) or to an independent anti-diabetic mechanism. Nonetheless, for an industry participant, *“this is a compelling clinical profile to develop as an add-on therapy to metformin for the prevention of cardiovascular risk.”*

Rather than positioning the medicine as a general glucose lowering agent, participants suggested focusing on a subgroup of patients, such as:

- Obese hypertensive diabetic patients, a group in which *“there is a real clinical benefit to be able to treat three additive factors”*
- Patients with microalbuminuria for whom a drop in blood pressure can be especially beneficial
- Patients at high risk of developing diabetes, because the profile suggests *“a pretty strong effect in terms of diabetes prevention and ongoing cardiovascular event reduction”*

Whatever the indication, development of this would likely be halted without early stakeholder consultation. Participants noted that the development program required for the third – prevention – indication would require extensive input from regulators and payers *“at an early stage to provide some assurance that if industry commits to a diabetes prevention study and the medicine does prevent events,”* then the value will be appropriately rewarded.

Seeking a glucose-lowering indication would be similarly risky so that *“the only way you would develop this is if you could get good input from regulators and payers pre-Phase III to say that they would approve this profile as an independent anti-glycaemic agent.”* In this dialogue, *“the question is what would be the indication ... The next question is what would be the reimbursement status.”* Additional assurance would be needed as to the appropriate clinical development pathway for demonstrating value in the desired indications.

Finally, participants discussed the question of appropriate comparators, agreeing that metformin is the appropriate comparator for this medicine only if it is considered for a first-line indication (unless the indication is in metformin-intolerant patients). If the medicine were positioned as an add-on to metformin, then its likely comparators would be placebo, or a second-line add-on to metformin (such as sulphonylureas, DPP-4s or TZDs). For a second-line indication on top of metformin, benefits on renal function and ventricular functions would be indicative of value.

Medicine profile “B”: A biological that may arrest disease progression

This profile presented a biological medicine that improves insulin secretion and has the promise of halting disease progression. It was characterised by the following value indicators and measures:

- An HbA1c reduction of 0.8%
- A durability of control that is steady (as compared to metformin, with which patients experience approximately a 0.4% increase in HbA1c each year)
- A better tolerability profile than metformin
- Administration by once-monthly injection
- Participants considered the impact on their assessment of a possible signal as to immune system compromise through elevations in upper respiratory tract infections
- Expected pricing of medicine B was a 20x multiple relative to metformin

This profile also indicated the necessity of early interactions with regulators and payers. Participants recognised that medicine B had the promise of halting disease progression, but demonstrating this benefit would require a multi-year data generation effort for which industry needs early consultation.

Participants first considered this profile without the immune system signal and suggested that *“it is the durability of control that is the real promise”* and that *“this is your pre-diabetes drug. This could actually stop diabetes before it developed.”* Medical experts praised the additional benefit of increased concordance that could be expected due to the medicine’s once-monthly administration.

An indication for prevention would require *“a lot of conversations with payers and regulators.”* An industry participant cautioned that, despite its promise, a drug with such a profile currently may not be developed because industry has no mechanism available for consultations to ensure

that a multi-year data development programme needed to demonstrate the medicine's effect in halting disease progression would lead to a higher price than that reimbursed at launch. And, given the high cost of producing a biologic, the achievable price at launch may not justify the investment. He asked, "*how do you get the confidence to develop that product at an early stage? How do you get the dialogue?*" He concluded that, while the high price of a biologic "*makes the payer argument quite challenging,*" the solution is to allow the price to rise if the medicine's benefits are proven.

Adding in the early signal of immune system impact to the profile greatly altered participants views of this medicine, with a medical expert observing that "*the possibility of immune system compromise with infection is a very big concern and a very bad point.*" An industry participant suggested that with, even a small number of debilitating infections, "*the drug would not get approved.*"

Medicine profile "C": A large HbA1c reduction with significant weight gain

The third profile presented a medicine with a large HbA1c reduction that comes at the expense of a relatively significant weight gain. It was characterised by the following value indicators and measures:

- An HbA1c reduction of 1.4%
- A weight gain of 2 – 5kgs, with those patients experiencing the largest reductions in HbA1c that had the greatest weight gain
- Expected pricing of medicine B was a 20x multiple relative to metformin

While participants appreciated the benefit of the large HbA1c reduction offered by this medicine, for most this attribute was largely overshadowed by the large gain in weight. For an industry representative, this profile would be considered only "*if it were completely safe with no hypoglycaemia.*" Even then, the weight gain in this profile raises "*a major compliance issue and a progression of disease challenge.*"

From the standpoint of drug safety, developers would be required to explain the mechanism causing the increased body weight as well as its potential health impacts. Of importance would be "*whether the weight gain will level off after six months ... or whether this really translates to 10 to 20 kg over ten years.*" In this context, participants agreed that while mode of action of a medicine may not be a major driver of reimbursement, "*it is important from the perspective of explaining its side effects.*" Interestingly, the concern with weight is not shared among all Member States, as, for example, "*the weight does not count for anything in the UKPDS.*"

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Appendix 3: Stakeholders start / stop matrix

Stakeholders behaviours to *Start*

	Industry	Medical Experts	Patient Advocates	Payers or Payer Adviser	Regulators
Industry	<ul style="list-style-type: none"> Explain better the economics of development Embrace comprehensive care approach Engage payers and regulators much earlier 	<ul style="list-style-type: none"> Accept industry involvement as part of patients' holistic care (e.g. Industry RNs working with practice RNS) 	<ul style="list-style-type: none"> Listen more to patients Accept need for holistic patient management 	<ul style="list-style-type: none"> Provide clearer roadmap as to criteria for value and pricing to justify development costs and choices 	<ul style="list-style-type: none"> Increase openness to epidemiological and observational data
Medical Experts	<ul style="list-style-type: none"> Embrace holistic approach in developing new drugs Aim for superiority in goals Help develop / implement evidence-based guidelines 	<ul style="list-style-type: none"> Increase adherence to treatment guidelines Share responsibility in patient care (collaborate effectively) 	<ul style="list-style-type: none"> Expand representation of patients 	<ul style="list-style-type: none"> Consider acceptance of surrogates Listen more to patients / customers 	<ul style="list-style-type: none"> Increase harmonisation with payers
Patient Advocates			<ul style="list-style-type: none"> Increase representation of the patient point of view in value indicators 		
Payers/ Payer Adviser/ Regulators	<ul style="list-style-type: none"> Focus on processes of care rather than on "the pill" 	<ul style="list-style-type: none"> Improve coordination between primary and secondary care 	<ul style="list-style-type: none"> Expand perspective beyond single disease area and advocate for broader representation of patients 	<ul style="list-style-type: none"> Embrace patient-centric perspective Be explicit and transparent in decisions 	<ul style="list-style-type: none"> Increase harmonisation with payers Increase process transparency

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Stakeholders behaviours to Stop

	Industry	Medical Experts	Patient Advocates	Payers or Payer Adviser	Regulators
Industry	<ul style="list-style-type: none"> Singular focus on individual medicines Secrecy and selectivity in sharing data 			<ul style="list-style-type: none"> Lack of willingness to raise prices if post-launch studies show added value Defining unmet need narrowly 	<ul style="list-style-type: none"> Defining unmet need too narrowly
Medical Experts	<ul style="list-style-type: none"> Developing several “me too” drugs in the same class Setting goals as merely non-inferiority to comparators 	<ul style="list-style-type: none"> Not listening to other members of patient care team 	<ul style="list-style-type: none"> Arguing on an anecdotal basis (should make more systematic arguments instead) 	<ul style="list-style-type: none"> Making decisions exclusively based on hard outcomes (takes 10 yrs+), thereby inhibiting innovation 	<ul style="list-style-type: none"> Relying only on RCTs to exclusion of physician experience / decisions
Patient Advocates			<ul style="list-style-type: none"> Using medical and scientific indicators as the one and only guidance 		
Payers/ Payer Adviser/ Regulators	<ul style="list-style-type: none"> Withholding of unfavourable data 	<ul style="list-style-type: none"> Lack of disclosure of conflicts of interests 	<ul style="list-style-type: none"> Negative “knee-jerk” reactions to broader involvement in the healthcare system 	<ul style="list-style-type: none"> Sending mixed and conflicting messages to industry 	