HOW IS THE VALUE PROPOSITION DRIVING THE DEVELOPMENT AND REIMBURSEMENT PROCESS IN MAJOR MARKETS?

What are the strategies and practical steps companies can take in development?

2-3 December 2014
Vancouver, BC, Canada

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

Report authors
Neil McAuslane, PhD
Lawrence Liberti, MSc, RPh, RAC
Tina Wang, BSc, MSc
Patricia Connelly, BA, ELS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK
Email cirs@cirsci.org
Website: www.cirsci.org

Report date: 20 December 2015

Section 1: Executive Summary

Background to the Workshop

Over the past decade, there has been rapidly increasing interest in the demonstration of value for health technologies and ongoing discussions about the definition, interpretation and measurement of value and innovation. In 2013, participants in the HTAi Policy Forum discussed the topic "HTA and Value" and concluded that most decision-making systems take into account similar elements to assess "value" and although these are assessed in different ways by different stakeholders, the impact on clinical benefits and harms were the primary elements. While the forum identified actions to improve alignment in definitions and assessment of value, the key areas remaining for debate are the identification of methods for building the relevant elements of value into drug development design and the underpinning components that demonstrate and effectively articulate the value of new medicines.

Constructing a value proposition has become the principal step for defining the need for a product in the marketplace. This needs to be integrated into a company's early decision-making processes as the value proposition provides an essential roadmap for a product's development and reimbursement processes. The evidence used to develop a value proposition helps position the new product against an established market leader or innovator by identifying significant endpoints of clinical differentiation and by capturing the benefit that matter most to patients, their doctors and society — such as symptom burden, financial costs, family disruption and ability to work. This involves ensuring the right information is collected during the clinical development phase and that companies can create dynamic Therapeutic Product Profiles that have a clearly stated value proposition to aid companies in their go/no go decision making.

This Workshop focussed on how companies need to be able to integrate their target stakeholders' different perspectives of value into their development decisions as well as using these insights to construct a viable value proposition to meet the needs of diverse stakeholders.

Workshop Objectives

- **Identify** the key elements and the evidentiary requirements of a robust value proposition in order to build it into the early drug development phase
- **Discuss** the key barriers for building the value proposition early into the development of new medicines and discuss the best approaches to address these challenges, including how, when and which stakeholders (health technology assessors, payers, clinicians and patients) need to be engaged
- **Consider** how companies can more effectively use the value proposition to drive their development strategies and address reimbursement challenges
- **Recommend** approaches for the development, evaluation and utilisation of value propositions in the era of value-driven healthcare systems

Introduction

Prof Robert Peterson, *Executive Director, Drug Safety Effectiveness Network Canadian Institute of Health* welcomed Workshop participants to Vancouver, saying that the focus of this meeting -- to identify the elements of the value proposition in pharmaceutical development and reimbursement -- mirrors the evolution in evidence-based medicine of two decades ago. He expressed the hope that these discussions would demonstrate that the development of value-based medicine and will incorporate all of the positive features of that evolution, to include at least some of the evidence requirements of the future.

Key points from presentations

SESSION: BUILDING THE VALUE PROPOSITION INTO DRUG DEVELOPMENT - WHAT ARE THE KEY ELEMENTS, CHALLENGES AND BEST APPROACHES?

Any framework for building the value proposition into drug development needs to incorporate an understanding of standard of care principles and health economic modelling and the potential impact of the product on length and quality of patient life and full care pathway costs as well as any other advantage. In addition, as detailed by **Nick Crabb,** *Programme Director – Scientific Affairs, National Institute of Care and Excellence*, one way to use health economic modelling to probe the issues of importance to HTA agencies and payers is to use the available early evidence to develop a multidimensional profile model that includes pricing to gain an early indication of a product's potential impact on length and quality of life and care pathway costs. These value-driven models could be used to derive a target product profile, which if met and adequately evidenced through clinical development would likely be considered favourably by HTA agencies and payers. The evidence would need to include health-related quality of life improvements, relative effectiveness, patient perspectives and impact on resource utilisation.

Context and perspective are key elements in the development of a value proposition for new drugs and technologies, and identifying the evidentiary needs to demonstrate value from the perspectives of different stakeholders is a primary consideration. **Dr Chander Sehgal,** *Director, CDR and Optimal Use of Drugs, Canadian Agency for Drugs and Technologies in Health* provided the perspective specific to payers, who require effectiveness data in addition to evidence of efficacy. Payers also seek an assurance of value for the health technologies they fund. However, issues of uncertainty can surround a new medicine at the time of its marketing approval including where it stands in relation to the current best available standard of care, whether it will fulfil an unmet medical need or where it fits into treatment paradigms. In addition, cost-effectiveness and hard clinical benefit, as opposed to surrogate outcomes, may not yet be demonstrated and the medicine's effect on quality of life or on sub-populations not studied in trials remains unknown, as does its association with rare but serious adverse events. Some of these uncertainty issues may be addressed through the use of real-world evidence and the use of integrated novel access paradigms such as adaptive licensing, which promises earlier access to important new therapies, moving from prediction to monitoring of a medicine's effects and from a binary to a more flexible and iterative process for approvals. In addition, International

cooperation in evidence development and risk sharing among stakeholders may help guide each group's tolerance around the gaps in evidence providing a framework to expedite access to critical new drugs and other first-in-class treatments.

As a *Public Member of the Canadian Drug Expert Committee,* **Frank Gavin,** provided the perspective of one who is tasked with identifying, weighting and applying values in health technology assessments on behalf of society. Mr Gavin identified quality of life as the most important factor in the creation of a value proposition for new medicines, saying that medicine developers should show good evidence of improved quality of life using carefully chosen and preferably validated outcome measures, especially in areas identified by patients and caregivers as important to the patient. Value propositions should also include information about the impact of the condition on caregivers including family finances, caregivers' ability to work and caregivers' health. HTA bodies, regulators and companies should find ways to include these impacts in their determinations of values and in their decisions.

Dr Gergana Zlatevam *VP, Payer Insights & Access, Pfizer* discussed the development of a value proposition for Eliquis (apixaban). Despite the fact that apixiban was the third novel anticoagulant to gain regulatory approval, it was approved with evidence of added value in clinical efficacy and safety in three indications. The company used both pre- and post-launch evidence to develop the value proposition for apixiban. The pre-launch evidence surrounded the burden of disease from both an economic and unmet need perspective and was derived from assessments that began in 2010 and that are still ongoing. The post-launch evidence focused on differentiating data on bleeding risk profile, stroke risk assessment and hospitalisation rates. Data for burden of disease, unmet need, analysis of treatment pattern data and indirect treatment comparison were used in the apixiban cost-effectiveness model and local adaptations were used for reimbursement submissions and price negotiations. As a result of local reimbursement/ payer evaluations, apixiban was approved for reimbursement in non-valvular atrial fibrillation in the US, UK, Germany, Italy, Spain, Australia and Canada.

Koen Torfs, *Global Reimbursement and Real World Evidence, Janssen* discussed the value proposition developed for canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor in the treatment of type 2 diabetes mellitus. The extensive clinical trial programme for canagliflozin included nine double blind randomised clinical trials; five clinical endpoints and patient-reported outcomes were measured at three different time points in at least six patient populations, yielding 810 short-term outcomes analysed using different statistical techniques. The results of these trials included a consistent dose-dependent reduction in HbA_{1c} for canagliflozin when administered as monotherapy, in combination with metformin, with metformin and a sulfonylurea, with metformin and pioglitazone and in combination with insulin. In addition, a substantial, sustained weight reduction was achieved versus glimepride. Some countries that base their evaluations on cost per quality-adjusted life years have accepted the full value proposition for canagliflozin, whereas health technology assessors in Germany focussed on the effects of canagliflozin in hypoglycaemia, which was one outcome in one trial. Experience accrued with canagliflozin suggests that there may be selective interest in outcomes and selective consideration of analytical methods and measurement time points by health

technology assessors and a holistic perspective for the evaluation of medicines was not observed. This experience resulted in overall uncertainty and questions as to the relevance and cost-effectiveness of complex modelling for new compounds.

Speaking on ways in which companies could embed value into the development process, **Dr James Murray,** *Research Fellow, Global Patient Outcomes and Real World Evidence Center for Expertise, Eli Lilly and Company, USA* first clarified that there are diverse objective and subjective definitions and measures of "value" for medicines, which may be viewed through the perspective of stakeholders that include the pharmaceutical industry, regulators, reimbursers, patients and healthcare providers. The employment of a value framework would enable the incorporation of those perspectives through use of a clear and consistent methodology for the assessment of value and allow agreement on how value is defined and actually used in decision making. This framework could be used to positively change the efficacy and cost-based framework that is often used in pharmaceutical development, regulatory and reimbursement decision-making processes. Through the use of value frameworks, subjective appraisals could be replaced with a more systematic, potentially qualitative and quantitative decision-making process. In addition, the probability that new medicines will meet both clinical needs and societal values will be enhanced if values are built early in the development cycle by using a framework to identify unmet clinical needs and the target population for those needs and to support economic modelling. Some elements of such a model can be added to the characterisation of medicines that are already in clinical development or review but the optimal time for the use of a value framework is at the beginning of a product's life cycle, when the first developmental decisions occur.

Historically, the concept of intellectual property protection incentivised investment and risk taking with less emphasis given to how to share the cost of innovation or a health system's ability to purchase the products. In addition, because of a range of financial environments, individual countries strike varying types of pricing relationships with manufacturers. **Dr Lou Garrison,** *Professor, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy; Adjunct Professor Departments of Global Health and Health Services, University of Washington* explained that the traditional economic model provides an incentive for manufacturers to seek a high price value at launch. Until recently, neither the private nor public sector has had incentives to collect data about real-world effectiveness of new medicines to validate the initial value proposition. However, today, society places a value of public good on the availability of information about the effectiveness of medicines. Across the world, there has been a movement towards integration of health systems and the most likely future scenario will see a growing robustness of data systems to support a move towards capitation of risk-based payments.

Developing a value proposition for new medicines that is relevant and compelling to a diverse group of stakeholders that now includes industry, regulators, health technology assessors and patients and their advocates is a complex art. Although the diversity of perspectives within these individual groups adds an additional layer of complexity to industry engagement with them, this interaction is critical to inform internal decision-making processes and to align internal research and development teams on a shared path forward. **Dr. Ludwig Steindl,** *Head of Strategic Access and Operations, Global Market Access, Bayer Pharma AG, Switzerland* offered that whilst there is no clear framework for industry to transition from its former single focus

on external engagements that facilitated regulatory success to those that include input from multiple stakeholders, it may be helpful to segment these engagements into three types, 1) pre-launch engagement to develop the core value drug proposition; 2) pre-launch engagement to explore healthcare system needs and expectations and 3) engagement post-launch and beyond to deal with any remaining uncertainties in value. To design clinical programmes to meet the needs of payers, industry-HTA dialogue to discuss technical payer perspectives on value proposition and data requirements needs to start at phase two at the latest. In the future, points of intervention along the R&D value chain should become a continuous dialogue to evolve the value proposition and to push the boundaries of health value.

Niklas Hedberg, *Chief Pharmacist, TLV – The Swedish Dental and Pharmaceutical Benefits Agency* outlined the engagement opportunities for stakeholders in the development of the value proposition saying that in the research and development phase, industry, regulators, health technology assessors, patients and payers may be engaged, typically during early advice meetings. The relevance of the input from some of these stakeholders is likely to vary according to the compound and the timing and circumstance of the discussion. During a standard registration, industry and regulators will typically be most engaged, although more stakeholders may be involved in novel adaptive licensing approaches since their alignment is an essential component. In addition to the development of a value proposition, a well-developed and recognised framework for achieving adaptive pricing may help ensure early access to new innovative medicines and enable cost control during the life cycle.

The health of patients and consumers is at the core of the value proposition for drugs. **Dr Katharina Kovacs Burns,** *Founding Member of the Canadian Best Medicines Coalition* said that as key stakeholders, patients should be engaged at the beginning and throughout the development of medicines. In addition to the potential for product loyalty and optimal pricing, the benefits of integrated patient engagement have been cited in multiple publications and include improved participation in clinical trials and even maximised medication adherence. Industry and agencies should have a defined strategy for patient engagement and should consider reaching out to patient or consumer groups through pilot programmes. Patient engagement should also include a plan for patient orientation and education regarding the development and rollout of new medicines. Recruitment criteria, restrictions and guidelines for patient involvement should be developed further. For patient advisory groups to be useful there needs to be well-defined criteria for both the selection of advisory group members and the parameters within which the group will work as well as provisions for a review of the group's effectiveness.

Having FDA approval no longer ensures primary tier market access to new products in the United States and multiple payers with differing standards are now increasing their demands for evidence of effectiveness and value. Like the regulation of medicine, there are multiple legitimate social objectives for the appropriate reimbursement of new therapies: these include ensuring equitable access to a new therapy, supporting the innovation process, while promoting safety, efficacy, effectiveness, value for money, cost-effectiveness and efficiency in medicine use. However, there is no single platform analogous to the FDA to support the sustained dialogue necessary to achieve those integrated objectives. The Green Park Collaborative programme, a multi-stakeholder forum to advance regulatory science through clarification of the evidence

expectations of public and private payers, is a forum that could advance reimbursement science and potentially help fill this vacuum. The Collaborative produces recommendations for study designs for specific clinical conditions, classes of interventions or methods and focuses on comparative effectiveness and value. **Dr Donna A Messner,** *Vice President and Senior Research Director, Center for Medical Technology Policy (CMTP), USA* discussed an example of a recent Effectiveness Guidance Document for studies of new therapies for type-2 diabetes.

Coordinated and hosted by the French Haute Autorité de Santé (HAS), as part of the EUnetHTA Early Dialogues, twelve HTA bodies and nine companies participated in ten pilots (two preparatory) in 2012-2013 for ten medicines in various therapeutic areas. Also coordinated by HAS, Shaping European Early Dialogues for health technologies (SEED) is an international consortium of fourteen EUnetHTA partners, funded by the European Union. SEED was developed to build on the EUnetHTA Early Dialogues experience and the ultimate objective was the development of two draft methodological protocols for early dialogues for drugs and medical devices. At the time of this Workshop, ten early dialogues for drugs and for medical devices or diagnostics/procedures were planned, with feedback from all participants and a proposal for a permanent model for early dialogue in Europe to be submitted for comment to EUnetHTA and the HTA Network. **Prof Finn Børlum Kristensen,** *Head of Coordinating Secretariat of EUnetHTA, Danish Health and Medicines Authority, Denmark* reported that at HTA 2.0 in Europe in 2014, it was agreed that network collaborations such as these have created value for participants, that positive national results of European cooperation have been demonstrated and that national synergies between policy making, HTA and regulation have materialised at the EU level, getting effective technologies faster to patients.

When **Patricia Furlong,** *Founding President and CEO, Parent Project Muscular Dystrophy (PPMD), USA* started the PPMD in 1994, Duchenne muscular dystrophy (DMD) was largely unknown and there was no standard of care, clinical infrastructure, advocacy or education. As a result of the lobbying efforts of PPMD, the Muscular Dystrophy Care Act was signed into law in 2001 and brought in much needed funding for DMD research. There is currently a rich pipeline of drugs at various stages of development to treat DMD through dystrophin rescue or replacement or to treat muscle loss, inflammation and fibrosis and cardiac issues and to impact the regulation of calcium. However, it is estimated that a lifetime of these therapies could cost three quarters of one million dollars per patient. In order to improve the existing structure and decision-making processes of regulatory and reimbursement organisations and expedite access to potentially important therapies, the PMD has engaged in multiple advocacy activities, including the PPMD Benefit-Risk Study to explore how parents and guardians of individuals with DMD prioritise risk and benefit in the context of new therapies and the development of draft guidance to industry for developing drugs to treat DMD, elements of which were later incorporated into draft guidance released by the FDA June 2015. This guidance has potential impact on all future submissions and reviews of Duchenne candidate treatments and is being viewed as a model and precedent for shaping the future by other advocacy groups for rare diseases.

Rosmin Esmail, *Director, SCN Health Technology Assessment and Adoption, Alberta Health Services, Canada* detailed issues surrounding the consideration of value from the perspective of the provider who

generally relies on a wide range of evidence and a wide range of views on value. The Network may also seek advice from expert committees or bodies, clinical experts, patients and patient organisations while also trying to balance patients' views with those of the wider public and balance the value gained by new technologies against the values lost through opportunity costs. The value proposition for new health technologies can be considered from the different levels within the structure of healthcare in Alberta. The macro level is represented by the payer, the Alberta Ministry of Health, the mezzo layer is represented by the provider, Alberta Health Services (AHS) and the micro level is represented by the AHS Strategic Clinical Networks. Providers may also need to take account of political or commercial considerations when decisions become the focus of public attention. The provider also needs to determine the unmet clinical needs, as well as the clinical and economic value and benefits that a new technology will bring to the patient, the payer, or society.

The final Workshop presentation was given by **Barbara J Sabourin,** *Therapeutic Products Directorate, Health Products and Food Branch, Health Canada*, who provided the value proposition for Health Canada, which employs a regulatory system based on the determination of quality, efficacy and safety throughout a product life cycle. The agency's regulatory system has changed in response to stakeholder needs and there are now a variety of available regulatory pathways that provide flexibility such as priority assessments, notice of compliance with conditions, extraordinary use new drugs, and orphan drugs. Health Canada can provide expertise as needed related to developing issues as pandemic flu, severe acute respiratory syndrome (SARS) or Ebola and it is now authorised to ensure that sponsors fulfil the terms specified in notices of approval with conditions. There is increasing interaction between Health Canada and Canada's health technology agency, the Canadian Agency for Drugs and Technologies in Health (CADTH). Evaluation processes and practices continue to evolve for Health Canada as they do for regulatory and HTA agencies globally, toward a system of evidence-based decisions, transparency and cooperation among partners and a lack of duplication. The goal of this evolution is timely access to safe effective therapeutic products.

Recommendations from across the Syndicates

1. To determine the value proposition for a medicine, agree on tools that are fit for purpose: When it is determined that a placebo-controlled trial is the best comparison, it must be executed in a way that facilitates the best possible multi-comparison analysis.
2. Patients should have a voice in trial design during drug development, and participate in health technology assessment and priority setting decision making.
3. Because of the potential of a medicine's value proposition to change throughout its lifecycle, adaptive approaches could be used to establish and revise prices based on real world evidence.
4. CIRS should conduct an inventory of current practices in patient engagement to identify best practices and principles.
5. Maximise and advance stakeholder engagement through innovative activities such as a multi-stakeholder collective that has a formal remit and is of long-term duration..
6. Mine social media and other sources of real world evidence for input on values or use it as a communication platform to increase awareness around the topic of the value of medicines.
7. Create a value assessment grid for each disease state that allows stakeholders to describe and weight the elements they feel contribute to the value of a medicine within a particular therapeutic area and help to develop a standard definition of value terms for that condition.

WORKSHOP PROGRAMME

DAY 1

SESSION: BUILDING THE VALUE PROPOSITION INTO DRUG DEVELOPMENT - WHAT ARE THE KEY ELEMENTS, CHALLENGES AND BEST APPROACHES?

Chairman's introduction	**Prof Robert Peterson,** *Executive Director, Drug Safety Effectiveness Network Canadian Institute of Health*
Development of a general framework for defining and assessing value	**Dr Nick Crabb**, *Programme Director for Scientific affairs, National Institute for Health and Care Excellence, UK*

Building value proposition for new medicines in drug development - What are the key elements and what needs to be considered?

HTA agency perspective	**Dr Chander Sehgal,** *Director, Common Drug Review and Optimal Use , CADTH*
Patient perspective	**Frank Gavin,** *Public Member of Canadian Drug Expert Committee, CADTH, Canada*

How can companies effectively use the value propositions for new medicines to make good development decisions?

Case study one	**Gergana Zlateva,** *Payer Insights & Access North America Lead, Pfizer Inc, USA*
Case study two	**Koen Torfs,** *Vice President, Global Reimbursement and Real World Evidence, Janssen NV, Belgium*
How could companies improve approaches to embed value into development process?	**Dr James Murray**, *Research Fellow, Global Patient Outcomes and Real World Evidence Center for Expertise, Eli Lilly and Company, USA*
Key economic consideration to address/manage the need to demonstrate value across jurisdictions	**Prof Lou Garrison,** *Professor and Associate Director, Pharmaceutical Outcomes Research and Policy Program, University of Washington, USA*

SESSION: EVALUATION OF THE VALUE PROPOSITION IN DECISION MAKING: MULTI-STAKEHOLDER INVOLVEMENT AND HOW TO MANAGE DIVERGENCE ACROSS JURISDICTIONS

How and when should different stakeholders be engaged to develop and test the value proposition during drug development and roll-out?

Company viewpoint	**Ludwig Steindl**, *Vice President, Head of Strategic Access and Operations, Global Market Access, Bayer Pharma AG, Switzerland*
HTA reflection	**Niklas Hedberg,** *Chief Pharmacist, the Dental and Pharmaceutical Benefits Agency (TLV), Sweden*
Patient Involvement	**Dr Katharina Kovacs Burns,** *Founding Member of the Canadian Best Medicines Coalition*

What are the current initiatives that can aid companies in identifying the evidence to support the value proposition and its role in innovation?

Green Park Initiative	**Dr Donna Messner,** *Vice President and Senior Research Director, Center for Medical Technology Policy (CMTP), USA*
Early scientific advice during development phase	**Prof Finn Børlum Kristensen,** *Head of Coordinating Secretariat of EUnetHTA, Danish Health and Medicines Authority, Denmark*

SESSION 3: SYNDICATE DISCUSSIONS

Syndicate A: How can the company ensure the value proposition plays a role through the lifecycle of the product?	**Chair: Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency* **Rapporteur: Dr Anke Hövels**, *Assistant Professor, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. The Netherlands*
Syndicate B: What is the best practice for engaging stakeholders to enable development of value proposition?	**Chair: John Sproule,** *Senior Policy Director, Institute of Health Economics, Canada* **Rapporteur: Nicola Allen**, *Research Fellow, CIRS*

DAY 2

SESSION: SYNDICATE DISCUSSIONS CONTINUED

Chairman's introduction	**Prof Robert Peterson,** *Executive Director, Drug Safety Effectiveness Network Canadian Institute of Health*
Syndicate feedback and discussion	
Panel reflection	
HTA perspective	**Prof Bruno Flamion,** *Professor of Physiology and Pharmacology University of Namur, Belgium*
Payer perspective	**Barbara Walman,** *Assistant Deputy Minister, Medical Beneficiary and Pharmaceutical Services, BC Ministry of Health, Canada*
Industry perspective	**Dr Sanjay Gupta,** *Head of HEOR, Daiichi Sankyo Inc, USA*
Patient perspective	**Lona Vincent,** *Senior Associate Director, Research Partnerships, Michael J Fox Foundation, USA*

SESSION: VALUE-BASED HEALTHCARE: HOW CAN THE VALUE PROPOSITION BE USED TO SUPPORT FURTHER HEALTHCARE REVOLUTIONS?

Working toward value-based healthcare systems

Patient perspective	**Patricia Furlong,** *Founding President and CEO, Parent Project Muscular Dystrophy, USA*
Payer perspective	**Rosmin Esmail,** *Director, SCN Health Technology Assessment and Adoption Alberta Health Services, Canada*
Regulatory perspective	**Barbara Sabourin,** *Director General, Health Canada, Canada*

Industry and HTA agency perspectives from the floor and general discussion

Section 2: Syndicate Discussions

Syndicate Discussion A

How can the company ensure the value proposition plays a role through the lifecycle of the product?	
Chair	**Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency*
Rapporteur	**Dr Anke Hövels**, *Assistant Professor, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. The Netherlands*

Background

A key area in the growing interest in the demonstration of value for health technologies is the identification of methodologies to ensure that the relevant elements of value are built into drug development design to demonstrate and effectively articulate the value of new medicines at launch and in the construction of a value proposition that defines the need for a product in the marketplace. This value proposition also needs to be integrated into a company's early decision-making processes as it provides an essential roadmap for a product's development and reimbursement processes.

The objectives of this Syndicate group were to:

1. Discuss the use of the value proposition in development and lifecycle decisions for a new medicine
2. Identify the practices that companies use or could use to ensure that the value proposition plays an important input into the development of new medicines so that companies can be certain that a drug's value proposition has been optimised at submission.

Questions for consideration

- What are the critical components in defining the value proposition? What does the value proposition look like; that is, is it a compilation document, an outline or is it based on target product profiles?
- At what stage of development do companies articulate the value proposition, how is this communicated internally and who is responsible within the company for generating and ensuring the proposition is integrated into development plans?
- What role does the value proposition play in the development decision-making process; does this differ depending on the stage of decision making and what are perceived as the main barriers and best practices for implementing the value proposition at each milestone?
    - Please consider the different stages of development and how the value proposition could aid decision making at critical development milestones (proof of concept, go/no go milestone decisions and decision to submit)

- How do companies currently involve the use of the value proposition at the various stages in the lifecycle? How might this change in the future; what factors may influence these changes?
- What practices do companies use or could use to ensure that the value proposition is embedded as a key component of the decision making process in development to ensure that the medicines that are developed are also reimbursed?
- What are the mechanisms to improve the development and use of the value proposition and what needs to be done in the short and long term to enable this to occur?

Results

This Syndicate based their discussion on the following definition of *value proposition*: The full potential of a product throughout the lifecycle to manage the needs of a given customer. A value proposition is flexible, could change over time and requires trust between stakeholders.

In this definition:

- *Potential* is ability of the product to produce a positive net health benefit. The product can also effect an economic differentiation or have a societal impact.
- *Needs* are strong evidence that the medicine has resulted in a clinically meaningful difference in a common core outcome measure.
- *Customers* are regulators, patients and their families, health technology assessors and payers and society or the healthcare system.

Critical issues

There are many different customers, each with different needs or requirements for a medicine. Part of the challenge in the development of a value proposition is the selection of common relevant outcomes measures without approaching each customer on an individual level. There may be a core customer around which the others can be grouped but if so, it remains to be determined how, when and where that customer should best be engaged to determine the full potential of product.

Appropriate patients should be involved in the development of a value proposition. In consideration of the involvement of patients in healthcare technology assessment, Health Technology Assessment International (HTAi) has developed *Values and Quality Standards for Patient Involvement in HTA*. Available at http://www.htai.org/index.php?id=630&tx_ttnews[tt_news]=400&cHash=d9a57a09252aaddf6e2c68a82ca8cc0f

Similarly, a framework for patient involvement in developing a benefit-risk profile has been promulgated by a US-based consortium (http://mdic.org/pcbr/framework-report/). The Syndicate agreed that the use of core measures that capture information required by all of these various stakeholders should be developed. These measures should incorporate benefits and harms for which we will have to assume a level of uncertainty. Better tools for indirect comparison are also required that would satisfy the various needs of stakeholders and allow multiple evidence requirements to be addressed through fit-for-purpose studies.

Recommendations

1. To determine the value proposition for a medicine, agree on tools that are fit for purpose: When it is determined that a placebo-controlled trial is the best comparison, it must be executed in a way that facilitates the best possible multi-comparison analysis.
2. Patients should have a voice in trial design during drug development, and participate in health technology assessment and priority setting decision making.
3. Because of the potential of a medicine's value proposition to change throughout its lifecycle, adaptive approaches could be used to establish and revise prices based on real world evidence.

Syndicate Discussion B

What is the best practice for engaging stakeholders to enable development of value proposition?	
Chair	**John Sproule,** *Senior Policy Director, Institute of Health Economics, Canada*
Rapporteur	**Nicola Allen**, *Research Fellow, CIRS*

Background

The concept of the *value* of a medicine is largely predicated on the stakeholder's frame of reference. A developer may see value in terms of filling a market need with an appropriate return on investment; clinicians may see value as the incremental improvement in the pharmacotherapy of a disease; a pharmacoeconomist might see value as the outcomes relative to their costs; patients may perceive value as improvement in their own health situation; others may see it as the impact on or based on a measure of societal health improvement.

Addressing the needs of key stakeholders in a consolidated way helps mitigate the main risks in drug development:

- a persistently disconcerting rate of discontinuation in Phase 3 due to lack of efficacy;
- failure to gain regulatory approval because the compound's risks are deemed not to outweigh its benefits;
- difficulty in achieving reimbursement for the requested price because the compound's profile has not be sufficiently well characterised to demonstrate "value" over existing therapies;
- commercial disappointment because of lack of product differentiation.

Therefore, the early, ongoing and balanced engagement of key stakeholders in the medicine development process is one way to establish a common goal, centred on the value proposition of the new therapy. However, multi-party engagement practices are in their infancy and best practices for these engagements are yet to be determined. This is particularly true when seeking to develop a common approach to building value into a new medicine. Therefore, this Syndicate was charged with investigating ways that can maximise the involvement of all stakeholders, to provide not only validation of development plans but also to identify ways that their input can result in a robust dossier with evidence that can justify to each stakeholder the value of a new therapy.

The objectives of this Syndicate group were to

1. Discuss the engagement with different stakeholders and how this can enable the development of a value proposition that meets the needs of the decision makers
2. Identify the best practices that companies use or could use to engage with different stakeholders to ensure that the value proposition has been optimised.

Questions for consideration

- How can these elements be built on to ensure stakeholder engagement to define the value of a new medicine?
- Is there a way to easily permit a stakeholder to explain what their concept of *value* is, as it will relate to the specific discussion in which they are involved?
- How can a company engender a research-centric culture that truly integrates multiple stakeholder viewpoints into the value equation?
- Is each contributing stakeholder organisation organised in a way that encourages collaboration and shared learning? If not, what recommendations can be made to strengthen the organisational structure?
- What is the course that a patient follows during the evolution of their disease? How will understanding what value patients put on specific aspects of their loss of health inform the role the new medicine will play in giving back value to their lives? How does this affect the evolution of the value perspective?
- How do healthcare providers such as physicians, pharmacists, investigators, geneticists contribute to creating a research plan that clearly distinguishes a new product's value from others?
- What role can professional organisations (patient representative groups, physician associations, HTA consortia) play? How can they best reflect individual and societal needs?
- Can a "toolbox" of best practices be developed from which various stakeholders can draw upon to develop a common approach to communicating their expectations of value? What would be the common elements?
- How should this toolbox of best practices be vetted, refined and communicated?

Results

For purposes of this discussion of the best methods to engage stakeholders in the development of the value proposition, it was suggested that this Syndicate consider a list of stakeholders that included clinicians; policy makers and regulators; healthcare providers; insurers, payers and purchasers; the life science industry; researchers; research funders; and patients and consumers. The Syndicate further refined that list by separating patients, citizens, caregivers and patient groups because of the key points of differentiation in the needs and perspectives of all of these subgroups.

They next discussed the potential definitions of *value* (Fig 1) and determined that the definition of value varies among stakeholders and within stakeholder groups and depends on the value preferences being considered; for example, clinical value, economic value or opportunity costs (Fig 2).

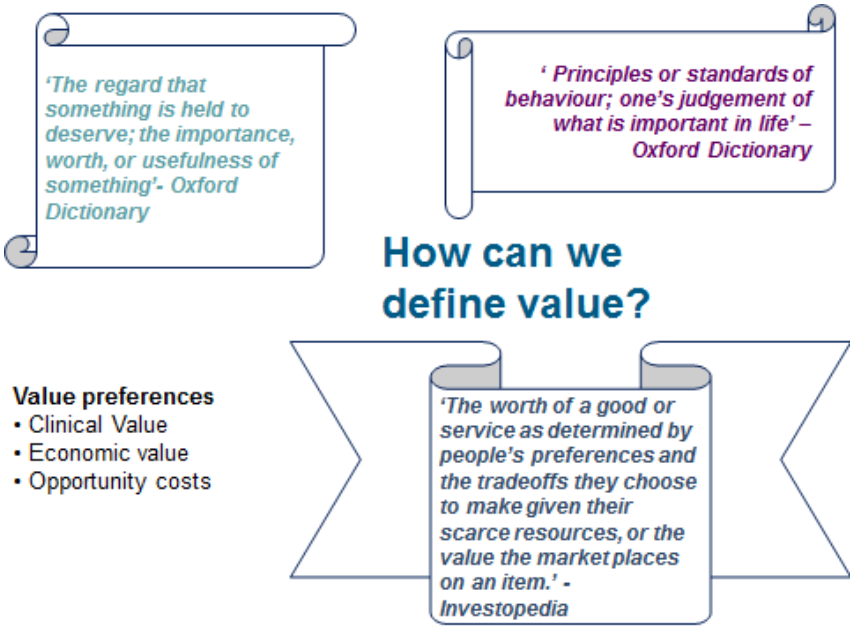

Figure1. Definitions of *value* will vary according to stakeholder perspective and value preferences that are considered.

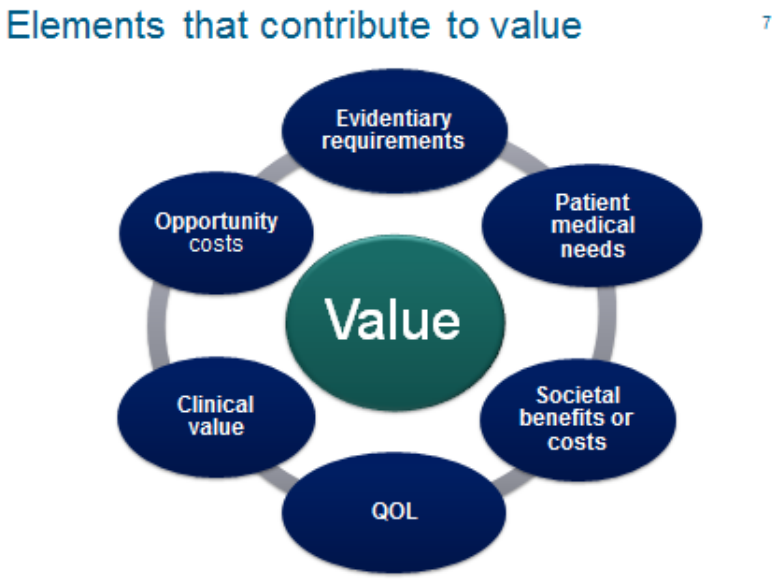

Figure 2. Many factors contribute to the value of a medicine.

These elements of value will change across the development cycle and according to the progression of disease.

Strategies

An inventory of existing practices for patient engagement should be conducted to identify best practices and principles. Among these practices, trust between stakeholders and trust of the stakeholders in science is primary. Bi-directional education will help improve health literacy among patients, caregivers and citizens and reduce incorrect assumptions regarding value among industry, regulators and health technology assessors. Transparency from industry and regulatory and HTA agencies will serve to increase learning and support trust (Fig 3).

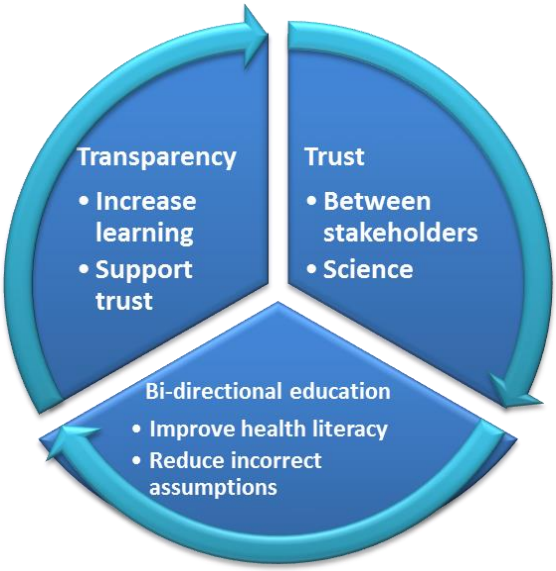

Figure 3. An inventory of current patient engagement practices would help to identify best practices and principles.

New approaches such as a collective of stakeholders that meet in workshops or on an online discussion group may encourage novel ideas for stakeholder engagement. Social media could be mined for input on values or could be used as a communication platform to increase education. Finally, identifying values by disease state could allow stakeholders to describe and weight the elements that they feel contribute to the value of a medicine within a particular therapeutic area and help to develop a standard definition of value terms for that condition (Fig 4). This could support initiatives such as the US FDA's Patient Focused Drug Development Initiative (http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm) and the Center for Medical Technology Policy (CMTP) Green Park Initiative.

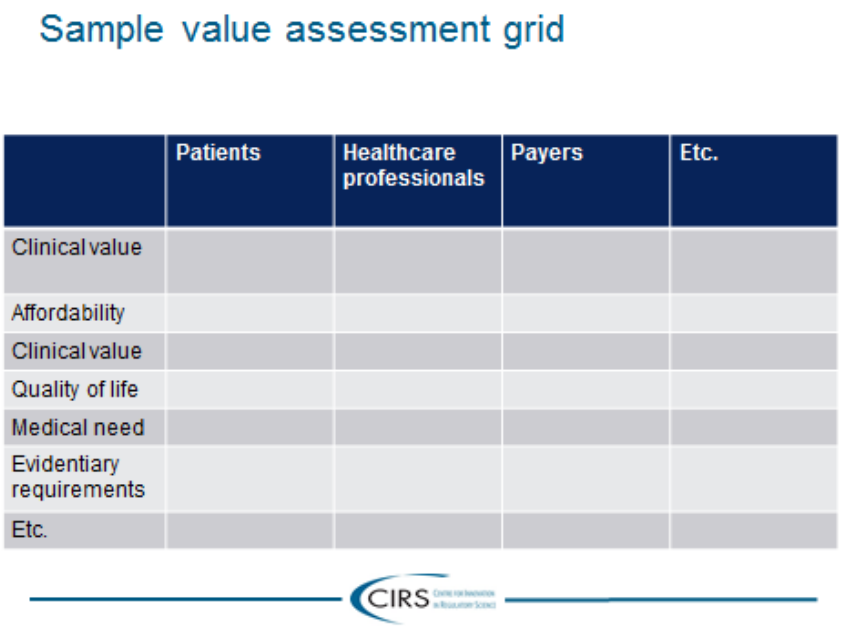

Figure 4. A grid could be created for the assessment of the value of a medicine according to the stakeholders in that disease state.

Recommendations

1. CIRS should conduct an inventory of current practices in patient engagement to identify best practices and principles.

2. Maximise and advance stakeholder engagement through innovative activities such as a multi-stakeholder collective that has a formal remit and is of long-term duration..

3. Mine social media and other sources of real world evidence for input on values or use it as a communication platform to increase awareness around the topic of the value of medicines.

4. Create a value assessment grid for each disease state that allows stakeholders to describe and weight the elements they feel contribute to the value of a medicine within a particular therapeutic area and help to develop a standard definition of value terms for that condition.

Section 3: Presentations

General framework for defining and assessing value

Nick Crabb, *Programme Director – Scientific Affairs, National Institute of Care and Excellence*

Early integration of stakeholder requirements

In order to be adopted and used effectively, new medicines must gain regulatory approval and be recommended for the appropriate cost-effective use by health technology assessment (HTA) agencies. . Ensuring that the views of these agencies are considered early in the product development process are important components of an efficient development process. This is particularly true today, when many new products are being developed by small-to-medium enterprises that may not have the level of resources and experience of major pharmaceutical companies and which can, therefore benefit from early agency input.

All HTA and payer agencies operate to efficiently allocate healthcare resources while ensuring timely patient access to new products; however, the decision-making processes employed by these organisations may vary. These processes encompass consideration of clinical effectiveness relative to current standard of care or the impact of a medicine on either length or quality of the patient's life; the specific cost effectiveness and cost effectiveness thresholds; and balancing patient and public input, social value views, legislation and whether there are any additional special considerations (Figure 5). These special considerations could include burden of illness, rare diseases or the potential for innovation to change current care practice.

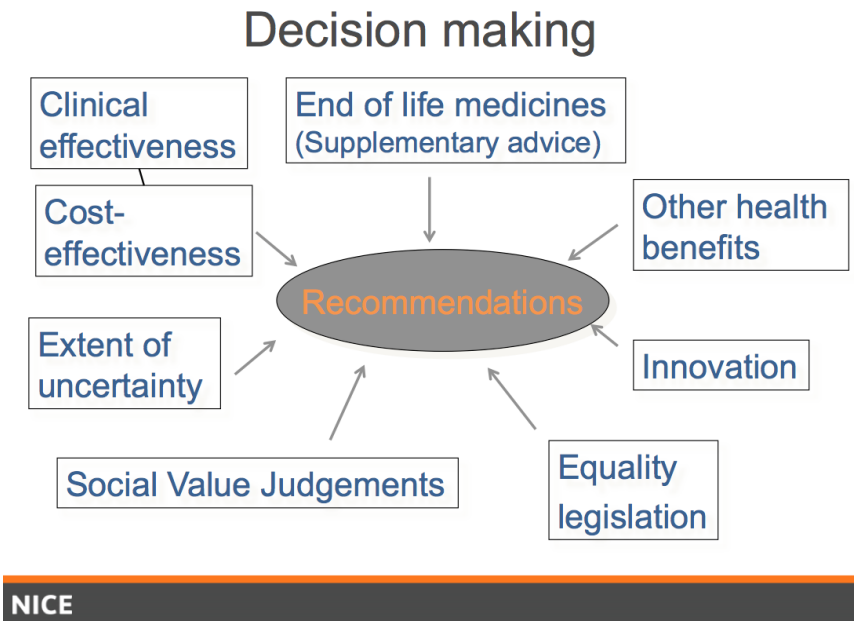

Figure 5. Factors affecting the decision-making processes of agencies responsible for reimbursement and usage recommendations of new pharmaceutical products with regulatory approval.

Representation of the cost-effectiveness analysis used by The National Institute of Care and Excellence (NICE) in its current decision-making process shows that the probability of a positive recommendation increases if the cost of a quality adjusted life (QALY) year is lower. However, products with higher QALY cost can be special cases that may be recommended for use if they extend life or improve the quality of end of life (Figure 6). Analysis of incremental cost-effectiveness ratios for technologies appraised by NICE between 2007 and September 2013 shows that 80% of products submitted received a positive recommendation, with a small number being positively valued under end-of-life provisions.

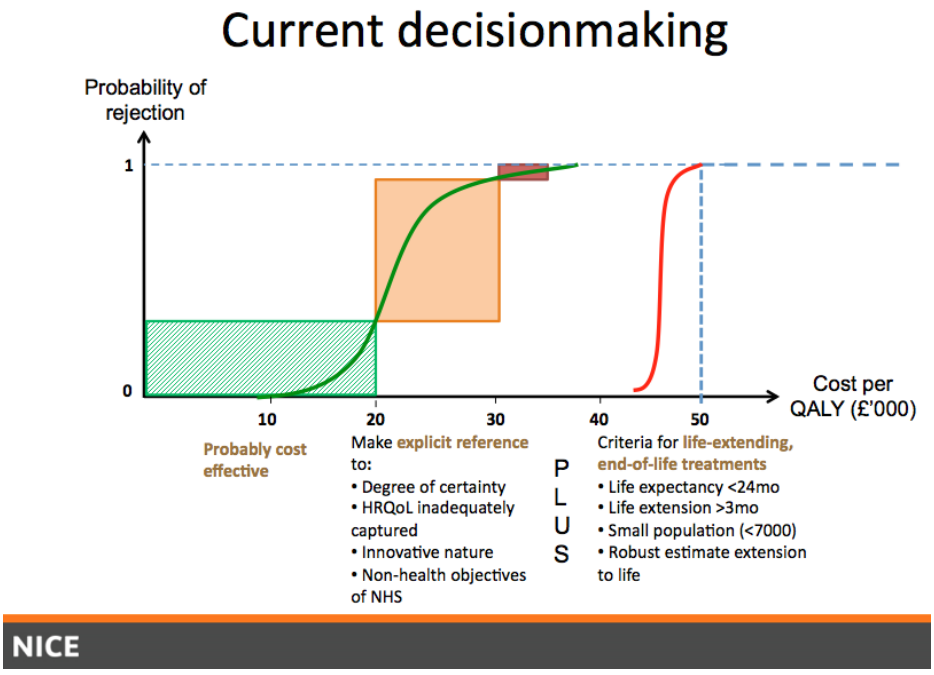

Figure 6. Factors affecting the cost-effectiveness analysis process used by The National Institute of Care and Excellence.

Healthcare resource allocation versus timely patient access

There are several regulatory initiatives that support earlier access in areas of unmet medical need including the European Medicines Agency adaptive licensing pilot programme and United Kingdom Early Access to Medicine Scheme. However, use of these pathways means that agencies such as NICE will likely have less available evidence on which to base their decisions and point to the need for a clear and balanced decision-making pathway, and the reliance on real-world post-approval evidence to reduce uncertainty over time.

Framework for building the value proposition into drug development

Any framework for building the value proposition into drug development needs to incorporate understanding of standard of care principles and health economic modelling and the potential impact of the product on length and quality of patient life. In addition, full care pathway costs as well as any other advantage of the product

need to be considered and well defined. As any of these factors could change during development, so there needs to be careful surveillance of developments that could alter the standard of care throughout the product development process (such as innovative products coming to market, transformative changes in clinical practice or the development of new treatment guidelines).

There are several ways health economic modelling could be used to develop models to probe the issues of importance to HTA agencies and payers in key target markets. One is to use the available early evidence to develop a multiple-product profile model that includes pricing to gain an early indication of a product's potential impact on length and quality of life and care pathway costs. These value-driven models could be used to derive a target product profile, which if met and adequately evidenced through clinical development would likely be considered favourably by HTA agencies and payers. The evidence would need to include health-related quality of life improvements, relative effectiveness, patient perspectives and impact on resource utilisation.

. . . use the available early evidence to develop a multiple-product profile model that includes pricing to gain an early indication of a product's potential impact on length and quality of life and care pathway costs.

While larger pharmaceutical companies have the resources to design necessary HTA evidence generation protocols into clinical development programmes, small-to-medium organisations may need to seek help and scientific advice to accomplish this goal. Advice can be obtained from many individual HTA agencies such as is available from the NICE scientific advice programme or from multiple HTA agencies such as is available through the European Network for Health Technology (EUnetHTA) Shaping European Early Dialogues (SEED) initiative. Parallel advice may also be sought from regulatory and HTA agencies under new pilot initiatives. Finally, funding support to build economics expertise may be available from trade associations or through sponsored programmes such as Innovate UK.

It has become increasingly important to find a balance between meeting growing healthcare needs with limited resources and ensuring timely patient access to new products that are clinically and cost effective. Understanding the perspectives of the decision makers for these medicines from the early stages of product development will enable these products to enter the armamentarium of healthcare resources earlier rather than later.

Building the value proposition for new medicines in drug development – what are the key elements and what need to be considered? An HTA perspective

Dr Chander Sehgal

Director, CDR and Optimal Use of Drugs, Canadian Agency for Drugs and Technologies in Health

Perspective and value

Context and perspective are key elements in the development of a value proposition for new drugs and technologies and identifying the evidentiary needs to demonstrate value from the perspectives of different stakeholders including regulators, health technology assessors, payers and patients is a primary consideration (Figure 7).

Like other stakeholders in the development, regulation and reimbursement of medicine, payers are faced with challenges that include fixed budgets versus growing and unpredictable workloads and sharp increases in incremental cost-effectiveness ratios for new drugs such as those for orphan diseases. When making funding decisions for new medicines; however, the evidence needs of payers are specific to their perspective and ideally include a requirement for effectiveness data in addition to evidence of efficacy. Because effectiveness data are usually not available, payers must rely on efficacy studies, which are designed to meet regulatory rather than payer informational requirements and do not typically include cost-effectiveness or patient group input and which may lack an active drug comparator.

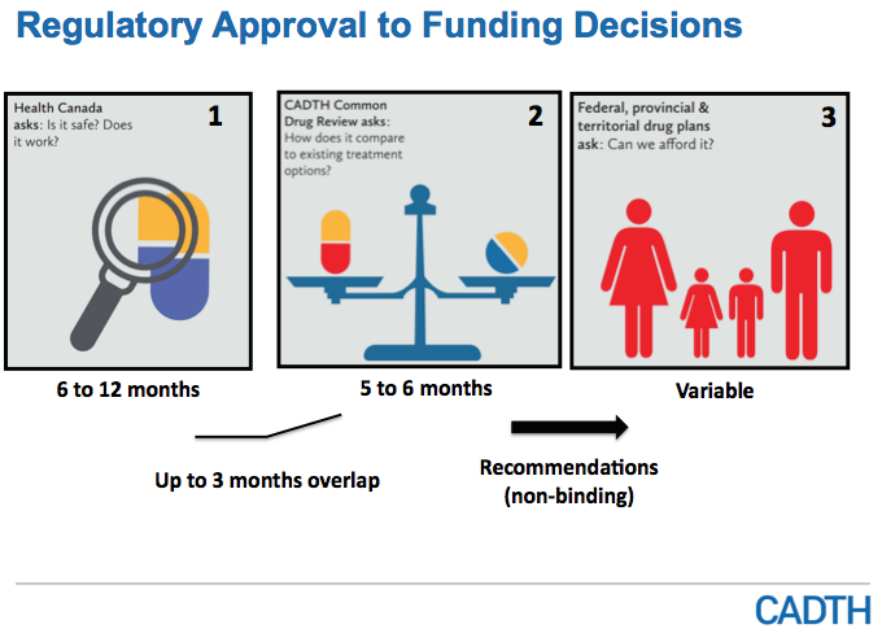

Figure 7. Differing questions asked by stakeholders in the regulatory, health technology assessment and funding decision-making processes for new medicines in Canada.

Uncertainty and adaptive licensing

Payers also seek an assurance of value for the health technologies they fund. However, issues of uncertainty can surround a new medicine at the time of its marketing approval including where it stands in relation to the current best available standard of care, whether it will fulfil an unmet medical need or where it fits into treatment paradigms. In addition, cost-effectiveness and hard clinical benefit as opposed to surrogate outcomes may yet to be demonstrated and the medicine's effect on quality of life or on sub-populations not studied in trials remains unknown as does its association with rare but serious adverse events.

Some of these uncertainty issues may be addressed through the use of real-world evidence developed in alignment with novel adaptive licensing approaches, which promise earlier access to innovative therapies (Figure 8), moving from prediction to monitoring of a medicine's effects and from a binary to a more flexible and iterative process for approvals and reimbursement. In addition, adaptive licensing may facilitate involvement of patients in the regulatory and reimbursement processes and lead to improved understanding of diseases, the introduction of innovative clinical trial designs, more targeted prescribing and better informed patient care decisions, maximising the positive impact of new drugs.

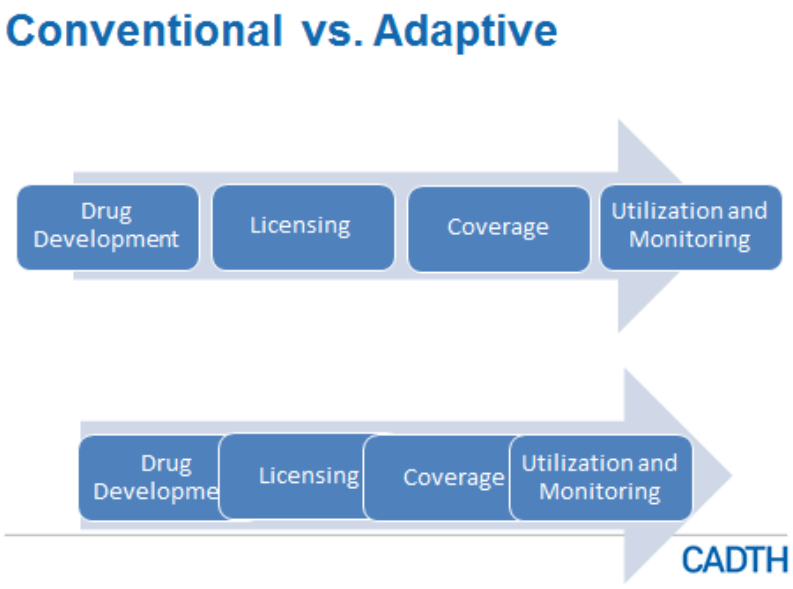

Figure 8. Overlapping timelines for medicine development, regulation and reimbursement in adaptive pathways may result in expedited availability of medicines.

Payers do have concerns about the adaptive licensing approach; it may be viewed as simply a method for faster drug listing and the apprehension that its implementation with limited payer involvement will increase the regulatory-reimbursement divide. Other concerns include the potential for increased off-label use of drugs, numerous implementation and monitoring challenges and the feasibility with associated "adaptive pricing".

Payers do believe real-world effectiveness and safety data can inform reimbursement coverage decision making. However, the methodological rigour and validity of real-world data may be called into question and their reliability, credibility and ownership remain challenging issues. In addition, extrapolating the results of broadly inclusive observational data may often be as problematic as extrapolating the results of narrowly focused randomised clinical trials and their collection represents a potential administrative burden to the healthcare system and could involve significant lag time. Furthermore, collecting real-world effectiveness data may also prove challenging to industry because of the associated cost, potential lack of return on investment and the risk that less favourable results may result in a product being relegated to limited use in or removed from formularies.

The way forward

Collaboration between payers and regulators is required to address the challenges presented by adaptive licensing approaches and plans for adaptive pricing, including downward adjustments for additional indications should be considered as an element of these procedures. International cooperation in evidence development and risk sharing has occurred in the United States with the Agency for Healthcare Research and Quality Effective Healthcare Program and in Canada with the Evidence Building Program of Cancer Care Ontario and British Columbia PharmaCare's Coverage with Evidence Development for Cholinesterase Inhibitors. These and other such initiatives may address gaps in evidence and expedite access to critical new drugs and other first-in-class treatments.

International cooperation in evidence development and risk sharing . . . may address gaps in evidence and expedite access to orphan drugs and other first-in-class treatments.

Identifying, weighting and applying values in HTA: A Public member's perspective

Frank Gavin

Public Member, Canadian Drug Expert Committee

Public and patient representation

It is now well recognised that there is a need for the patient perspective to be considered during the development and regulatory and HTA review of new medicines and the role of patient representatives in these activities has been largely accepted by society. However, the role of *public members* within these activities has yet to be established and there is no consensus about what societal values they should represent or how to measure them and there is no established relationship between public and patient perspectives and values.

Although they are not *patient* representatives, *public* members may be able to shed light on some common, yet incorrect assumptions regarding patient perspectives, such as the perception that people who share a diagnosis and their caregivers also share a common understanding of their main needs and goals. To the contrary, rather than assume there is one representative patient, it is important to listen to many patient voices. Another false conception concerns the existence of an inherent hierarchy of disease. Although some conditions may be more urgent or more threatening and the patients more in need of more expensive resources at a given time, an equal degree of attentiveness to all should be adopted and a focus on fairness and a commitment to equity maintained.

In any HTA value assessment it is important to consider the overall picture and examine the relationships between any person or organisation with which the patient has contact, such as family, community organisations, school, respite care agencies and any individual healthcare professionals as well as the relationships among all these stakeholders. That is, any HTA evaluation of a new therapy must consider that therapy in relation to other therapies and to the totality and complexity of the patients' and families' lives (Figure 9). Value propositions should be sensitive to such contexts.

Important elements of value propositions

The most important factor in a value proposition is quality of life and all assessments should show good evidence of improved quality of life using carefully chosen and preferably validated outcome measures, especially in areas identified by patients and caregivers as important to the patient. It should also include information about the impact of the condition on caregivers including sometimes overlooked items such as family finances, caregivers' ability to work and caregivers' health. HTA bodies, regulators and companies should find ways to include these impacts in their determinations of values and in their decisions.

. . . all assessments should show good evidence of improved quality of life using carefully chosen and preferably validated outcome measures, especially in areas identified by patients and caregivers as important to the patient.

Patient groups and manufacturers often assume cost savings to patients, families and the healthcare system will result from a new therapy, when there is no clear evidence these savings will eventuate. Any new therapy will likely affect the availability of or need for other therapies and services and any anticipated savings to the healthcare system, for example, less need for therapy x, fewer hospitalisations or less need for surgery, must be incorporated into the value proposition and explained in detail. Savings to patients and families should also be included. Value propositions must include the benefits that matter most to patients and the reason the degree or size of the benefit is sufficient to matter.

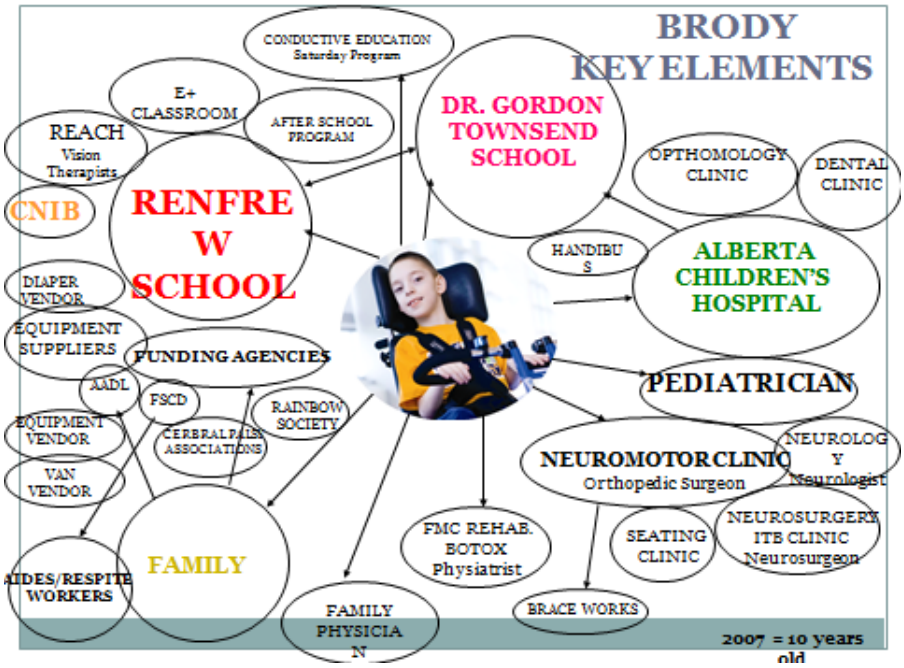

Figure 9. The interrelated relationships of the elements of one patient's care. Presented by F Gavin with permission of Joanne and Robin Ganton.

Societal values and patient preferences

The importance of societal values should also be considered when preparing a value proposition and propositions, recommendations and decisions should identify the relevant societal values and indicate their relative importance and weight. These values might include those placed on specific patient ages or abilities or on treatments for rare or life-threatening conditions.

Patient preference is often cited along with efficacy, safety and cost effectiveness as a value that informs recommendations or decisions. However, the term "patient preference" covers a wide range of situations from preference for a non-drug over a drug therapy to the more complex assessment of a therapy that reduces pain but may hasten death. In addition, the term rarely includes any ranking of values or identification of their relative weights; in general, more specific terms should be used. In contrast, while suffering is a defining

element of most experiences of illnesses, it is not often mentioned other than by patients and families and is difficult to gauge, although it is captured by some quality of life measures. Suffering should be recognised as key to understanding patient experience and should be made part of any value proposition.

The need for a framework

Assessors of new medicines need a framework and a process that incorporates values in decision making. This framework should include greater openness to different kinds of evidence, especially qualitative and new measures to capture kinds of quantitative information that has not been traditionally gathered. There is a need for more candour in communication with patients and patient groups and some acknowledgement that as humans we recognise and seek out an understanding of each other's values.

How can companies effectively use the value propositions for new medicines to make good development decisions?

Dr Gergana Zlateva *VP, Payer Insights & Access, Pfizer*

Macroeconomic realities, including unemployment, gross domestic product growth, debt and total healthcare expenses play an important role in determining budget allocations for healthcare and add a layer of complexity to industry's efforts to project a potential return on their investment in research in a disease area ten years into the future. Proving value for money is a prerequisite for market access to innovative medicines. That proof should consist of a compelling evidence base (including effectiveness in real-world settings) for superiority of a medicine compared with the standard of care across multiple customer audiences with various evidence expectations. However, formulary access and reimbursement for a new medicine is a function of the evolving evidence base, clinical and competitive environment and is likely to change over the time. In addition, the assessment of a new technology is likely to require "defensible pricing" for a given clinical effect relative to less expensive comparators, addressing the likelihood of capitated budgets and the growing need to address social value from a public health perspective. Furthermore, evidence will be evaluated differently in different global markets and sometimes a local value proposition will be based on factors in addition to clinical evidence, such as reliability of supply, localisation of manufacturing quality and capacity, and the ability to educate healthcare professionals on the new healthcare technology.

The development of a compelling, evidence-based value proposition and pricing construct is a process with numerous iterations in which various functional lines in a pharmaceutical company contribute to the development of evidence in parallel and in series during the lifecycle of a product. Evidence must be developed to demonstrate unmet need including epidemiological analyses to map prevalence and diagnosis rates and real-world data to evaluate the current standard of care, treatment patterns and cost of care. Evidence must also prove clinical need and value through an optimal study design with appropriate comparators, trial duration, endpoints and outcomes, target population, the use of acceptable quality measures, appropriateness for clinical guidelines and expected use in medical practice. Economic models must be developed to assess cost-effectiveness, and evidence needs to answer questions such as in which patients the therapy will be used, what is its added value versus existing options and what the benefits are for patients, caregivers, providers, payers and society (Figure 10).

The development of a compelling, evidence-based value proposition and pricing construct is a process with numerous iterations in which various functional lines in a pharmaceutical company contribute to the development of evidence in parallel and in series during the lifecycle of a product.

Case study: Experience with development and approval of apixaban

Despite the fact that Eliquis (apixaban) was the third novel anticoagulant to gain regulatory approval, it was approved with evidence of added value in clinical efficacy and safety in three indications, first, a reduction in overall mortality, a reduction in the risk of systemic embolism and stroke and a reduction in bleeding in the

prophylaxis of venous thromboembolism (VTE) in orthopaedic surgery. Second, by demonstrated efficacy in nonvalvular atrial fibrillation and third, by efficacy in VTE treatment.

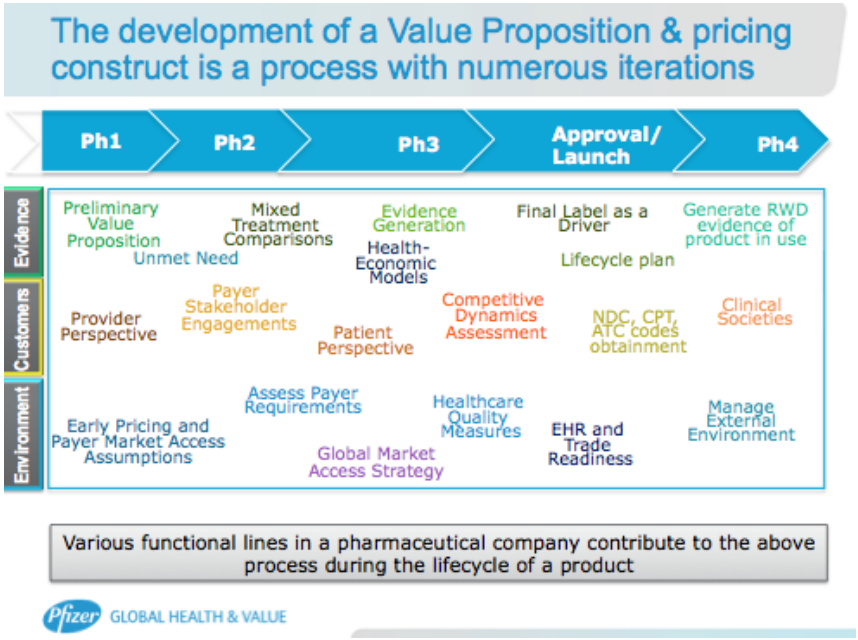

Figure 10. The development of a compelling, evidence-based value proposition and pricing construct is a process with numerous iterations.

The company used both pre- and post-launch evidence to develop the value proposition for apixaban. The pre-launch evidence focused on the burden of disease from both an economic and unmet need perspective and was derived from assessments that began in 2010 and that are still ongoing. The post-launch evidence focused on differentiation data on bleeding risk profile, stroke risk assessment and hospitalisation rates and was derived from assessments that began in 2013 and that are still ongoing (Figure 11).

Data for burden of disease, unmet need, analysis of treatment pattern data and indirect treatment comparison were used to populate the apixaban cost-effectiveness model and local adaptations were used for reimbursement submissions and price negotiations. As a result of local reimbursement/payer evaluations,

apixaban was approved for reimbursement in non-valvular atrial fibrillation in the US, UK, Germany, Italy, Spain, Australia and Canada.

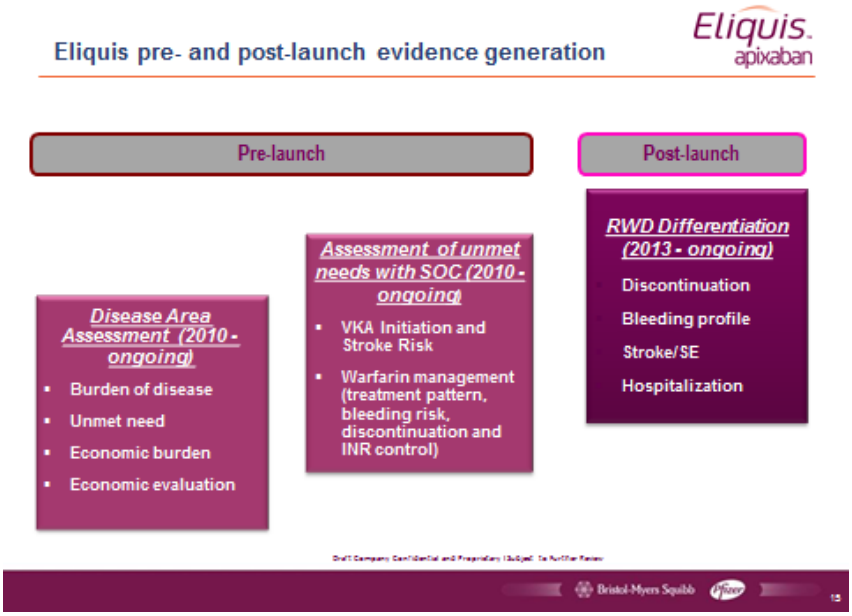

Figure 11. The value proposition for apixiban was developed with pre- and post-launch evidence.

Value propositions, development decisions and strategic planning:
Case study for canagliflozin

Koen Torfs, *Global Reimbursement and Real World Evidence, Janssen*

A value proposition can be defined as the full potential of a product or service to manage the needs of a given customer, supported by robust and credible data that is scientific, defendable and transparent in the context of regulatory and evidentiary requirements, real or perceived budgetary restrictions and the mixed reactions toward innovation among some key stakeholders.

A value proposition was first developed in 2007 for canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor in the treatment of type 2 diabetes mellitus. The therapeutic rationale for canagliflozin centred on its ability to improve plasma glucose levels with associated weight loss. At plasma glucose levels of ~180 mg/dL in normal healthy volunteers, renal tubular glucose transport is completely resorbed by SGLT1 and SGLT2 in the proximal tubule. At a plasma glucose level of >180 mg/dL; however, renal tubular glucose transport is saturated and urinary glucose excretion is increased in direct proportion to the plasma glucose concentration. By reducing SGLT2 activity, an inhibitor will lower the maximal renal transport of glucose, resulting in increased urinary glucose excretion, which could result in decreases in plasma glucose HbA_{1c}.. In addition, because caloric loss occurs with increased urinary glucose excretion, SGLT2 inhibition may also result in weight loss.

Weight loss was an important feature of the value proposition for canagliflozin because research among patients with diabetes revealed that whilst the medical value of diabetes therapies focussed on control of HbA_{1c} levels, patients would assign a greater value to those therapies that were effective in weight control with the associated positive impacts on physical functioning, quality of life and emotional well-being. Research among payers demonstrated that beyond simple HbA_{1c} reduction, delayed progression of disease, sustained efficacy and beta cell preservation were all top unmet needs and that whilst decreased macrovascular complications were highly valued, data on delaying microvascular complications might be easier to prove and would be accepted. Payers valued improved therapy compliance but improved effectiveness would also need to be proven.

The extensive clinical trial programme for canagliflozin included nine double blind randomised clinical trials of which three were actively controlled. Five clinical endpoints and patient-reported outcomes (Figure 12) were measured at three different time points in at least six patient populations, yielding a large number of short-term outcomes.. The results of these trials included a consistent dose-dependent reduction in HbA_{1c} for canagliflozin when administered as monotherapy, in combination with metformin, with metformin and a sulfonylurea, with metformin and pioglitazone and in combination with insulin. In addition, a substantial, sustained weight reduction was observed compared with glimepride (Figure 12). Furthermore, a potential value proposition could be hypothesised for the use of canagliflozin inhibitor in patients with higher body mass indices who become refractory to metformin as researchers have concluded that the progression to insulin therapy leads to much higher cost of care.[1]

Differing countries have various perspectives on value and when evaluating these results, the United Kingdom, Sweden and the Netherlands, which base their evaluations on cost per quality-adjusted life years have accepted the full value proposition for canagliflozin, whereas health technology assessors in Germany focussed on the effects of canagliflozin in hypoglycaemia, which was one outcome in one trial. The product eventually received a negative reimbursement recommendation there because canagliflozin was not studied as a monotherapy versus metformin, the main competitor in Germany and because there were limited data available for dose titration.

Conclusions

Experience accrued with canagliflozin suggests that there may be selective focuses in outcomes among health technology assessors and that assessment of some new medicines may follow the letter rather than the spirit of evidence-based medicine. A holistic perspective for the evaluation of this medicine was not always observed and with some jurisdictions there was a limited opportunity for conversation between stakeholders. This experience resulted in uncertainty discussion within the company as to what extent complex modelling for new compounds is relevant, useful or an appropriate financial investment.

Selective consideration of analytical methods and measurement timepoints was applied in this case, despite frequent calls by agencies for long-term data.

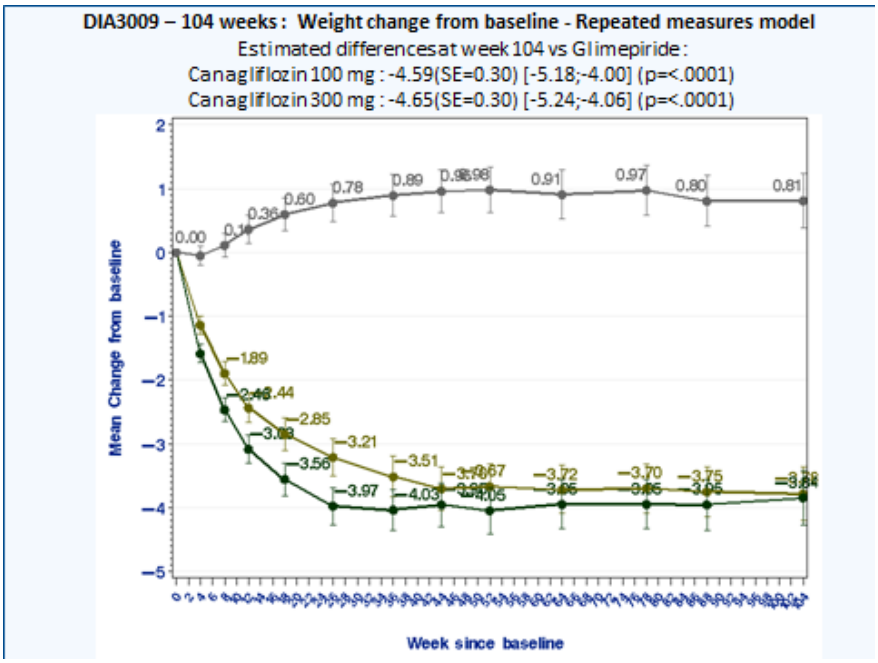

Figure 12. Weight loss observed with the use of canagliflozin compared with glimepride.

Reference

1. Guelfucci F, Clay E, Abllea S et al. Impact of therapy escalation on ambulatory care cost among patients with type 2 diabetes. *BMC Endocrine Disorders*. 2013l 13:15.

How could companies improve approaches to embed value into development process?

Dr James Murray, *Research Fellow, Global Patient Outcomes and Real World Evidence Center for Expertise, Eli Lilly and Company, USA*

Value frameworks

There are diverse objective and subjective definitions and measures of "value" for medicines, which may be viewed through the perspective of stakeholders that include the pharmaceutical industry, regulators, reimbursers, patients and healthcare providers. The employment of a value framework would enable the incorporation of those perspectives through use of a clear and consistent methodology for the assessment of value and allow agreement on how value is defined and actually used in decision making. This framework could be used to positively change the efficacy and cost-based framework that is currently used in pharmaceutical development and reimbursement decision-making processes. Through the use of value frameworks, subjective appraisals could be replaced with a more systematic, potentially qualitative and quantitative decision-making process. Agreement on the health gains that are the goals of new medicines is part of the development of a value framework, including the assessment of clinical or surrogate outcomes, patient-reported measures or quality of life improvements.

The issue of costs is an important and complex factor of value frameworks and as with value, the ways in which costs matter and are measured are also subject to individual perspective (Figure 13). It should be recognised that costs for one stakeholder represents savings or revenue for others and affordability and transparency around pricing have emerged as critical concerns in the measurement of value.

Which Costs Matter? To Whom?

Categories/Examples and Possibilities	Payers	Society	Patients/Caregivers
Costs	• Fees/Price (e.g., Fee schedules, AWP, etc.) • Administrative (e.g., labor, operations, filling fees, etc.)	• Incentives • Tax Breaks, etc. • Direct Investments in Infrastructure, R&D support,	• Premiums • Copayments/Co-insurance • Deductibles • Coverage Limits
Cost Offsets or Savings	• Averted costs in other health cost centers (e.g., medical, hospitalization, etc.) • Administrative efficiency (e.g., time saved, reduced fill fees, etc.) • Discounts • Rebates • Societal Cost Share • Patient Cost share	• Averted Work Loss • Productivity • Labor gains • Exports/Revenue • Intellectual property rights? • Innovation?	• Insurance • OOP Max • Subsidies (employer paid insurance) • Averted Work Loss • Tax breaks
WTP for Intangibles/Contextual Considerations	• Ex: Perceived quality and value	• Ex: Cultural norms, economic philosophy, etc.	Ex: Patient preferences, values, Leisure Time, and so on….

Figure 13. Variable perspectives on costs, savings and willingness to pay for new medicines.

Identifying unmet need and economic modelling

The probability that new medicines will meet both clinical needs and societal values will be enhanced if values are built early in the development cycle by using a framework to identify unmet clinical needs and the target population for those needs, which are then reflected in economic modelling.

Biomarkers, genetics, patient characteristics and the use of patient-reported measures can predict the heterogeneity of a treatment effect; further, there are variables such as interactions between multiple variables that are predictive of differential response to the same treatment by different patients. In addition, some factors that affect response can only be determined after a drug is approved and used in real-world settings such as variability in clinical practice, the influence of treatment guidelines, the prevailing standard of care, patient knowledge about the disease and its treatments, lifestyle influences and adherence to a treatment regimen. These factors will impact the effects of treatment and can explain the gap that sometimes exists between a product's efficacy in clinical trials and its real-world effectiveness (Figure 14). It remains to be determined how these variables can and should be weighted in making treatment, reimbursement and access decisions.

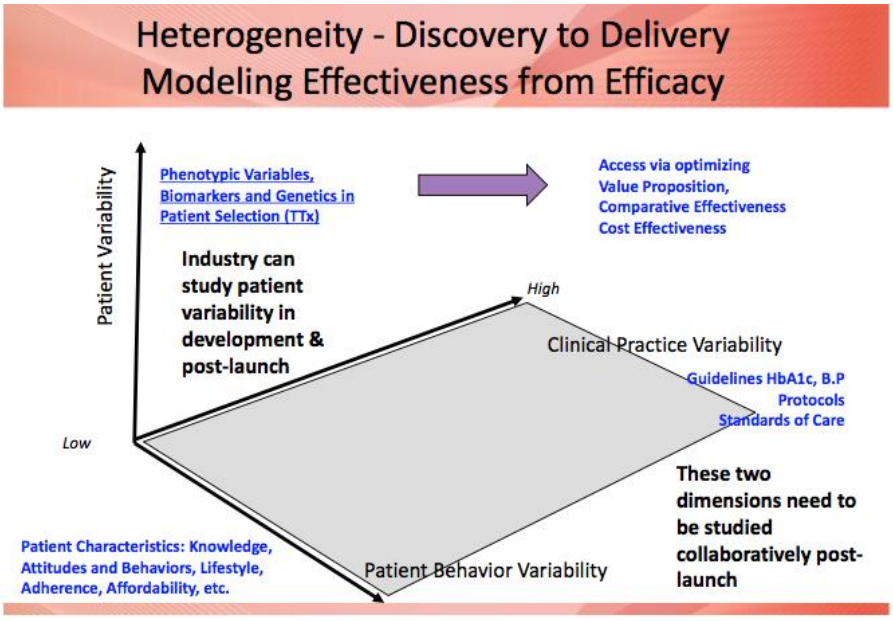

Figure 14. Heterogeneic variables that can explain difference between efficacy and effectiveness.

Value frameworks can facilitate the construction of early economic modelling, which incorporates the analysis of cost effectiveness and cost impact and models real-world effectiveness from clinical trial efficacy. Modelling can determine the probability of commercial success for a potential medicine and aid in decision making throughout the development process, including go-no-go and disinvestment decisions, decisions on price and product labels as well as reimbursement and access strategies.

There is a need for pharmaceutical companies to agree to quickly adopt a structured value framework for new medicines that will ensure that the perspectives of patients and caregivers, society, healthcare professionals, reimbursers and payers are used in the decision-making process regarding the safety, efficacy and effectiveness, value and affordability of new products. Some of these elements can be used to inform the progress of products already in clinical development or review but the optimal time for the use of a value framework is at the beginning of a product's life cycle, when the first developmental decisions occur.

. . . the optimal time for the use of a value framework is at the beginning of a product's life cycle, when the first developmental decisions occur.

How is the value proposition driving the development and reimbursement process in major markets?

Dr Lou Garrison

Professor, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy; Adjunct Professor Departments of Global Health and Health Services, University of Washington

Drug development forces and trends

It was recognised as early as 1993 that the pharmaceutical industry could benefit from pharmacoeconomic input early in the development process for new medicines.[1] In the more than two decades since that time international pharmaceutical companies are still trying to maximise the financial return on their investment in research and development subject to three key constraints. These factors influence trial design and regulatory focus:

- Patent life, which remains more or less fixed at 20 years, fixes the period of rewards, providing a powerful incentive for manufacturers to reach the market as quickly as possible.
- Price and reimbursement environments are often inflexible but there is increasing pressure on payers to obtain value for money spent—and thus for manufacturers to deliver and demonstrate the "value proposition." The global pricing environment has become more challenging because of external reference pricing, particularly in the European Union.
- The United States, with a "free" and generally unregulated pricing environment still offers the biggest rewards for new products, creating great pressures to design a product that will succeed in the US market and to get to market there as soon as possible..

Only a small proportion of drugs under development will make it to the market and the rapidly rising cost of developing new medicines was recently estimated at 2.6 billion US dollars.[2]

Historically, the concept of intellectual property protection has incentivised investment and risk taking without allowing for a way to appropriately share the cost of innovation. The payer negotiates the price for a medicine, bearing the risk that its incremental benefits will be worth the additional cost. Although payers are free to collect post-launch data, manufacturers have shown limited interest in doing so. In addition, because of a range of financial environments, individual countries strike varying types of pricing agreements with manufacturers. This framework provides an incentive for manufacturers to seek the highest justifiable price at launch but today, much of the world is seeking reduced pricing and even in the United States there is a push for justifiably lower prices. Up until now, neither the private nor public sector has had incentives to collect real world effectiveness data about new medicines. However, society now places a value of public good on both availability of medicines and availability of information about their effectiveness.

. . . society now places a value of public good on both availability of medicines and availability of information about effectiveness of medicines.

Economic value

The *value* of a new medicine can be considered as what fully informed patients would be willing to pay, usually via insurance, based on 1) any cost savings; 2) life years gained; 3) improvements in quality of life or morbidity; 4) productivity gains; 5) reduction in uncertainty due to accumulated real word evidence ; 6) improvements in adherence and uptake; 7) innovation; and 8) an option value (for example, survival creates an option to benefit from future advances). The emphasis on these elements of value can vary internationally (Figure 15) which may also focus on less frequently recognised values such as wider societal impacts, unmet needs, process issues, and cost savings beyond healthcare.

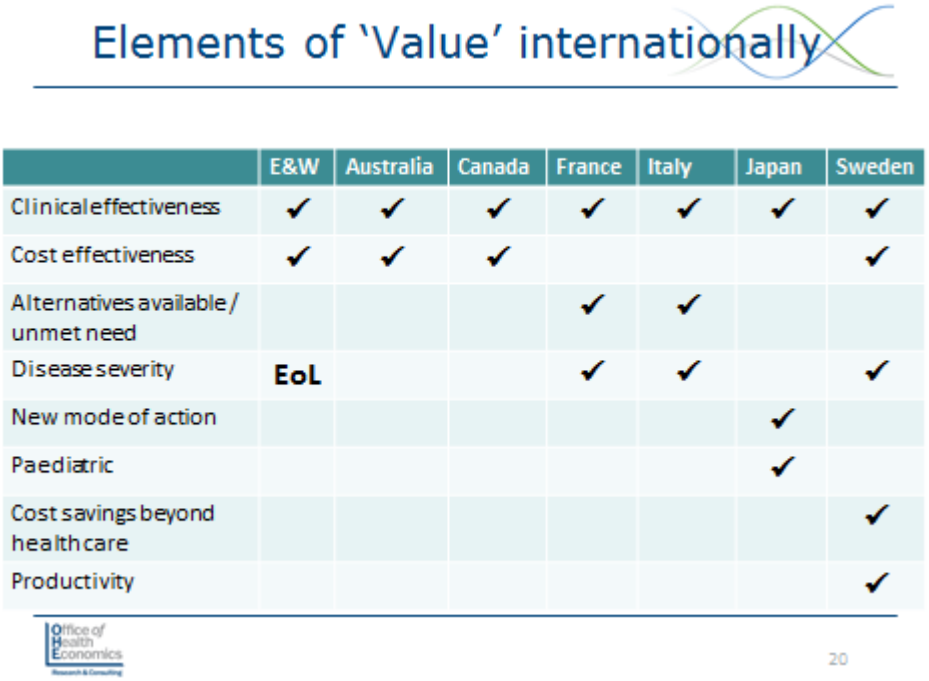

Figure 15. The necessary features of value for new medicines vary globally. E&W = England and Wales.

These value features can be measured; for example, the health effects of a medicine can be measured through the calculation of quality-adjusted life years gained or improvements in clinical or patient-related outcomes. They can also be evidenced; for example, the evidence of health effects can be collected through the use of randomised clinical trials, observational studies, clinical opinion or patient testimony. They can also be valued or rated through the use of population or patient values or categories or discrete scales

Anticipating the future for comparative effectiveness research

In the evolution of better evidence generation in Europe, closer economic relations between and among countries and coordination between health technology assessment agencies and the European Medical Agency has been envisioned. More coordination and collaborations across large registries and private-public partnerships are also needed and approaches such as adaptive licensing may help to meet rising pressures for earlier access to new products with appropriate reimbursement. In the United States, there has been a

movement towards integration of health systems and the most likely future scenario will see increases in the sophistication of these integrated data systems and a move towards capitation of risk-based payments. Although no major regulatory reform seems likely, there is the possibility that early access in the US could be further enabled using adaptive pathways and that post-launch evidence could be exchanged between Europe and the United States.

References

1. Clemens K, Garrison LP Jr, Jones A, Macdonald F. Strategic use of pharmacoeconomic research in early drug development and global pricing. *Pharmacoeconomics.* 1993;4:315-322.

2. Tufts Center for the Study of Drug Development. Costs to develop and win marketing approval for a new drug is 2.6 billion. Available at http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Accesses September 2015.

How and when should different stakeholders be engaged to develop and test the value proposition during drug development and roll-out? Company viewpoint

Dr. Ludwig Steindl, *Head of Strategic Access and Operations, Global Market Access, Bayer Pharma AG, Germany*

Pre-launch engagement to develop the core value drug proposition

There are multiple approaches to consider when engaging multiple stakeholders, including indirect methods such as local, national and multinational advisory boards and direct methods such as engagement with a national HTA agency or multiple national HTA agencies, alone or with national or multinational regulatory organisations. However, most current industry- HTA interaction takes place during the regulatory submission phase and these engagements seem to result in global diverse advices in value assessments for new medicines, even from HTAs of similar archetypes. To design more effective clinical programmes to meet the needs of payers, industry-HTA dialogue to discuss technical payer perspectives on value proposition and data requirements needs to start at phase two at the latest (Figure 16).

In addition, in anticipation that payers and external stakeholders will increasingly want to see patient-relevant value, industry needs to understand the issues that matter to patients. In recognition of the invaluable input that patients can provide, industry has made important inroads into vital patient engagement. Examples of these engagements include conducting patient interviews to understand the burden of cardiovascular disease, convening patient advisory boards to identify the barriers to receiving cancer care and better understanding the effects of treatment. Despite these inputs, informed quality of life and patient-reported outcome endpoints are playing a limited role in driving HTA/payer decision making.

Pre-launch: Exploring healthcare system boundaries

Between 2004 and 2010, hospitalisation and care of the elderly were primary factors in the increase of healthcare costs in Europe, whilst the cost of medicines was responsible for only 14% of growth. Thus, in order to unlock value in healthcare, a systems perspective is required rather that a narrow focus on a single aspect, such as drug therapy. The new models of drug development that will reduce costs and speed up patient access to medicines require broad stakeholder alignment. In the current regulatory-HTA scenario, treatment populations grow rapidly after licensing and the treatment experience contributes little to evidence generation and value substantiation. In a potential new scenario with adaptive licensing, the number of treated patients grows more slowly after the initial license is granted and evidence generation and value substantiation could be regarded as a continuum. It remains to be resolved, however, how much initial uncertainty stakeholders are willing to accept and what the dynamic pricing and reimbursement

In the future, points of intervention along the R&D value chain should become a continuous dialogue to evolve the value proposition and to push the boundaries of health value.

mechanisms will look like. In the future, the R&D value chain should become a continuous dialogue to evolve the value proposition and to ensure that maximum value is being obtained from the health system (Figure 17).

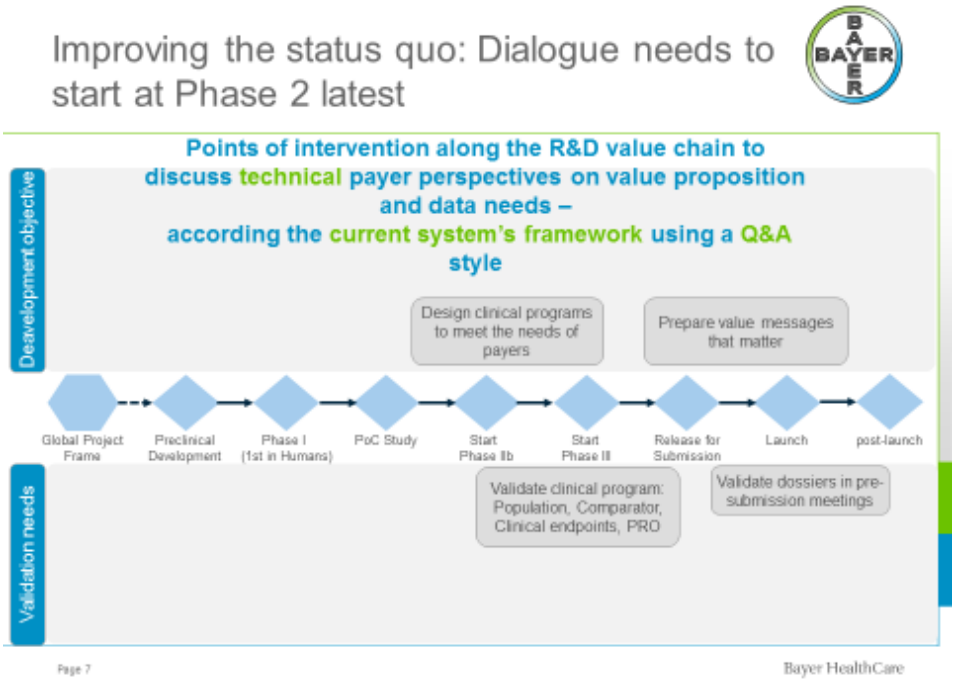

Figure 16. Industry-stakeholder engagement must start by phase 2 in the development of a new medicine.

At launch and beyond: Dealing with value uncertainty

Payers' may have multiple questions around a new approved medicine: what is the appropriate diagnoses and who are the target populations; how does this medicine fit into existing treatment pathways; what are the optimal regimens and treatment durations; what do real-life outcomes look like. From a reimbursement point of view, there are a broad range of options that can be employed to reflect those uncertainties including traditional approaches that offer discount rebates, volume pricing and cost sharing; risk-shifting conditional market access financial agreements; cost/volume caps; and outcomes-based risk sharing in which payment is based on real world treatment results. Globally, many companies have used outcomes-based approaches and this type of pricing will possibly have a growing role in the future.

Early and regular dialogue between regulators, health technology assessors, payers, patients and industry is needed along the lifecycle of medicines development to foster mutual understanding of remits, demands and constraints, to define value components and optimise evidence generation to substantiate and capture value, to ensure healthcare's innovation agenda maximises the use of resources within societal healthcare systems.

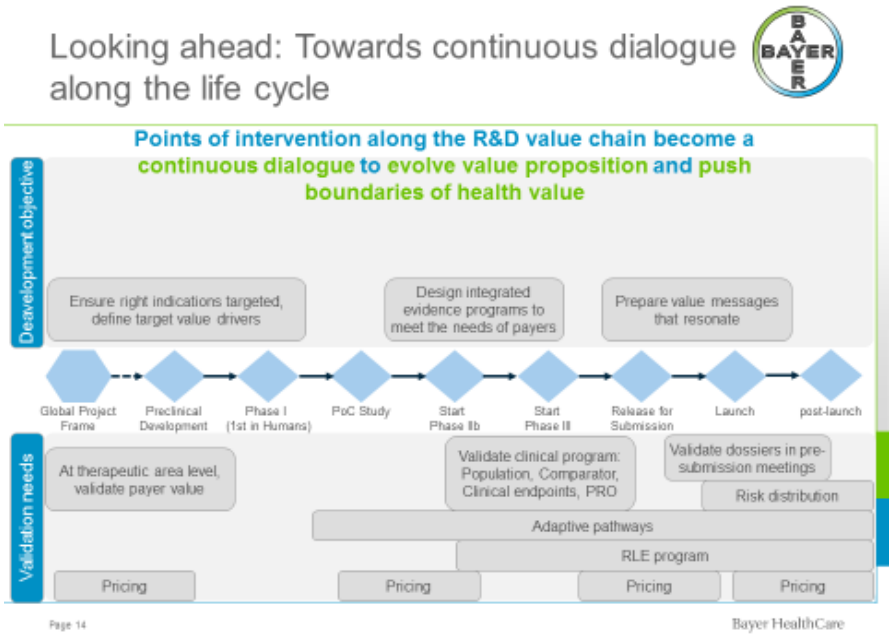

Figure 17. Moving forward, industry-stakeholder engagement must occur throughout the life cycle of a medicine to optimise the value proposition.

How and when should different stakeholders be engaged to develop and test the value proposition during drug development and roll-out?
- Health Technology Assessment perspective

Niklas Hedberg, *Chief Pharmacist, TLV –*

The Swedish Dental and Pharmaceutical Benefits Agency

Tandvårds- och läkemedelsförmånsverket (TLV) is the Swedish Government Agency under the Ministry of Health and Social Affairs, which decides on pricing and reimbursement of pharmaceutical products and medicinal consumables, the pharmacy retail margin for reimbursed medicinal products and consumables, the reimbursement of dental care, and regulates the generic substitution system. Whilst TLV decides whether a pharmaceutical product or dental care procedure shall be reimbursed by the state, twenty-one county councils provide healthcare with a high degree of autonomy and pay for in-hospital pharmaceuticals; the state funds the county councils for pharmaceuticals that are reimbursed.

Certain HTA agency practices are crucial for efficient introduction and utilisation of new medicines. One such practice is the use of registries. Although Sweden is fortunate in the availability and use of registry data there is still a need to optimise the use of existing data to fill in information gaps such as the reasons for prescribing a new medicine. Other critical HTA practices include having an open dialogue and the sharing of joint scientific advice early in the development process. Furthermore , negotiations for managed entry agreements must be developed among all relevant stakeholders using principles of flexibility and trust.

Challenges faced in pharmaceutical development, utilisation and financing

There are many challenges faced by stakeholders in the development, use and reimbursement of medicines including the fact that many new medicines are niche products and may be expensive to develop and produce or are being developed for small patient populations, leading to high per patient costs. Additional challenges include the fact that flexible pricing structures that facilitate the introduction of effective pharmaceuticals require data from follow-up studies that are increasingly important in pricing and reimbursement decisions while the growing number of biosimilars present opportunities for pricing competition. Furthermore, differences between efficacy in clinical studies and effectiveness in clinical practice may not be observed and from a financial perspective, payers may be charged more than is appropriate for some drugs while, because of budget constraints, some new, efficient drugs are used far less than they should be. These scenarios are complicated by the observation that there is a lag time to introduce some new medicines in Sweden and an uneven distribution of these across the country.

Ongoing work at TLV

Today, in an effort to meet and overcome these challenges, a platform of collaboration has been established with the TLV and all county councils. During the autumn of 2014, three-party agreements were initiated between pharmaceutical companies, TLV and the county councils and at the time of this Workshop in December 2014, a pilot was ongoing in the joint assessment of three products by TLV and county councils. In

addition, TLV is co-operating with the MPA and county councils to develop a Swedish model for adaptive pathways to patients to ensure managed introduction of new products without the addition of new decision-making processes (Figure 18). This model, which will ensure that pharmaceutical companies involve county councils at the early scientific stage fits well with TLV work to develop a pricing model.

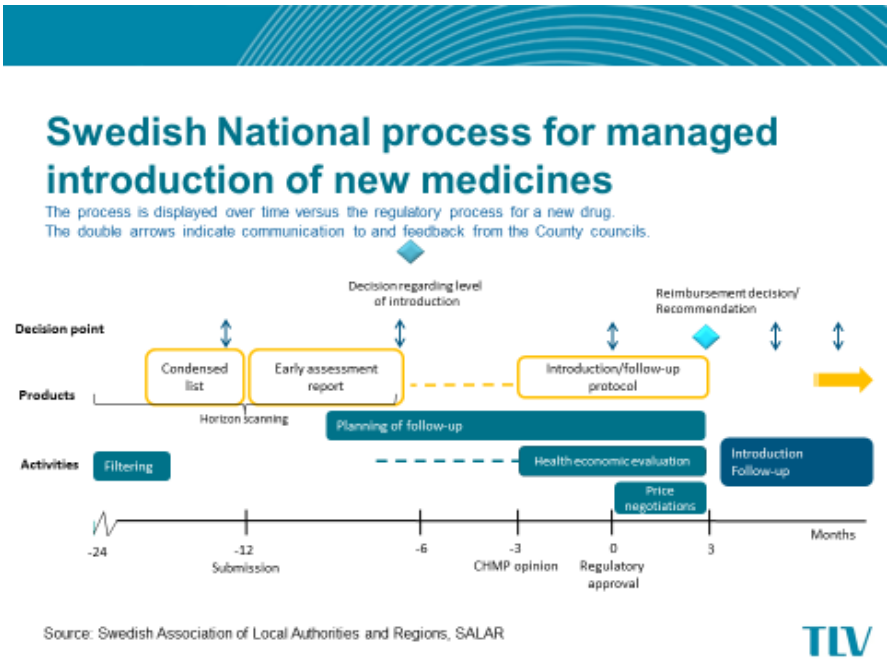

Figure 18. TLV is cooperating with the MPA to develop a Swedish model for adaptive pathways.

An adaptive pricing model for the future

> . . . a well-developed and recognised framework for achieving adaptive pricing will enable good cost control during the life cycle of new medicines and help ensure their early access.

Rational pricing for medicines is needed, particularly in the early phases of use when real world experience may be limited. Cost effectiveness is a key factor that needs to be monitored throughout the life cycle of a medicine and value-based utilisation built on value-based pricing is the desired result of this pricing model. When new events occur in the life cycle of a medicine such as a new indication, competition, new knowledge of cost effectiveness or significant changes in sales, a new evaluation of price will occur, sometimes in collaboration with county councils. For some medicinal products there will be many new events and for some none at all. It is envisioned that a well-developed and recognised framework for achieving adaptive pricing will enable good cost control during the life cycle of new innovative medicines and help ensure their early access.

How and when should stakeholders be engaged?

In the research and development phase, industry, regulators, health technology assessors, patients and payers may be engaged in developing the value proposition, typically during early advice meetings. The relevance of the input from some of these stakeholders is likely to vary according to the compound and the

timing and circumstance of the discussion. During a standard registration, industry and regulators will typically be most engaged, although more stakeholders may be involved in adaptive licensing since the timeframe for registration is extended. During the period of financing, healthcare technology assessors, payers and industry will have major roles and during utilisation and follow up, almost everyone (industry, regulators, health technology assessors, healthcare providers, payers and patient organisations) will be engaged in monitoring a medicine's value proposition (Figure 19).

Figure 19. The engagement of stakeholders in the development of the value proposition for new medicines.

Patient involvement in developing and evaluating the value proposition in decision making

Dr Katharina Kovacs Burns, *Founding Member of the Canadian Best Medicines Coalition*

Patients at the core of the value proposition

Despite a wide range in stakeholder perspectives regarding the value proposition for new medicines, there are certain points of consensus. It is agreed that whilst that assessment of *value* and *innovation* are different for different people, value can be broadly defined as outcomes compared with total costs. It is further agreed that a value proposition needs to be defined to guide the development and rollout of a new medicine, that patient health and health outcomes are at the core of that proposition and that the impact of a medicine on safety and harm are its primary measures. Because patients are the natural centre of the health system, a medicine's value proposition should identify the measures that matter the most to these stakeholders, set against a background of unmet need. As such, the proposition should provide useful and valuable guidance for the product's development and roll-out to patients.

Although patients have been part of the development of new medicines in the past as participants in clinical trials, there has been little meaningful engagement with them or with their advocates regarding the development process itself or the research questions that are used to develop evidence. In fact, most patients who agree to receive treatment have no knowledge of the evidence, or values, assessed in the development of the treatment. Patients need to know what data have been developed for a product and whether that data includes health outcomes that matter to patients, doctors and society (Figure 20).

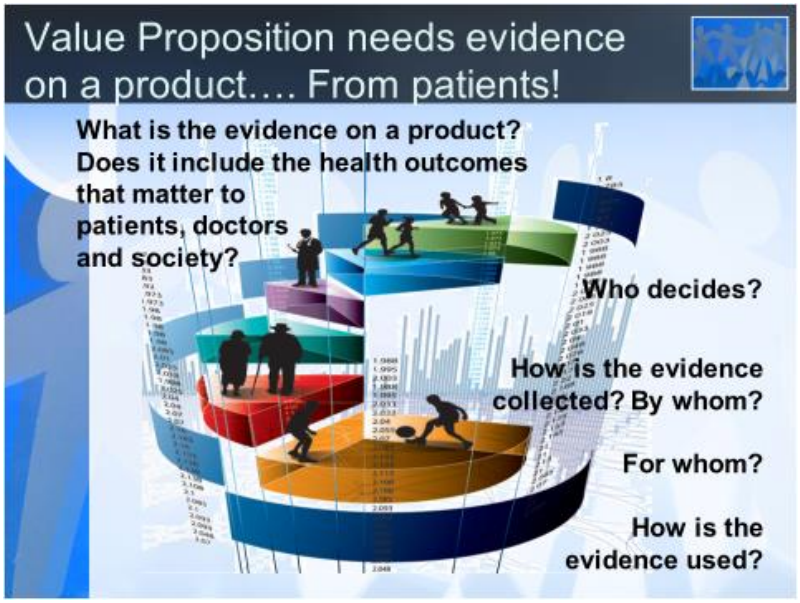

Figure 20. As key stakeholders in new medicines, patient engagement in development should include knowledge about and participation in the development of evidence.

In addition, agencies assessing evidence on a new product need to know that the information being presented for review includes a patient perspective at all stages. The point of view of patients and their families should be considered by regulators and health technology assessors when balancing issues of cost with quality of life and length of life. If the value proposition contains an assessment of risks associated with a product, those at risk should be identified, consulted and acknowledged.

If the value proposition contains an assessment of risks associated with a product, the holder of those risks should be identified, consulted and acknowledged.

Patient engagement strategy

Industry and agencies should have a defined strategy for patient engagement and should consider reaching out to patient or consumer groups through pilot programmes. Patient engagement should also include a plan for orientation and education to be provided for patients regarding the development and rollout of new medicines. Recruitment criteria, restrictions to and contracts for patient involvement should be developed. For patient advisory groups to be useful, there needs to be well-defined criteria for both the selection of advisory group members and the parameters within which the group will work as well as provisions for a review of the group's effectiveness.

Patients and consumers identify the value and need for medicines and patients and their health are at the core of the value proposition for drugs. As key stakeholders, patients should be engaged at the beginning and throughout the development of medicines. In addition to the potential for product loyalty and optimal pricing the benefits of integrated patient engagement have been cited in multiple publications and include improved participation in clinical trials and improved adherence to medication regimens.

Better evidence for decision making: The Green Park Collaborative Program

Dr Donna A Messner, *Vice President and Senior Research Director,*
Center for Medical Technology Policy (CMTP), USA

Regulatory and reimbursement science

The US Food and Drug Administration (FDA) has defined regulatory science as "the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of all FDA-regulated products." The agency further established its goal to "advance regulatory science to speed innovation, improve regulatory decision-making and get products to people in need . . . [and] to protect and promote the health of our nation and the global community."

There are several legitimate social objectives for the regulation of medicine including the assurance that marketed products are safe and effective; the promotion of rapid patient access to promising new products; the stimulation of life sciences innovation and the minimisation of burden on the developers of new medicines. These objectives can create tension with respect to evidence standards but regulatory science provides an opportunity to develop a scientific framework that reflects multiple legitimate competing views but the regulatory process must be inclusive, sustained, transparent, and iterative. The FDA provides the natural platform to support this process.

However, having FDA approval no longer ensures market access to new products in the United States and multiple payers with differing standards are now increasing their demands for evidence of effectiveness and value. Like the regulation of medicine, there are multiple legitimate social objectives for the reimbursement of therapies including equitable access to new therapy, support for innovation, the promotion of safety, efficacy, effectiveness, and ensuring value and cost-effectiveness. However, there is no single platform analogous to the FDA to support the sustained dialogue necessary to achieve those objectives. The Green Park Collaborative Program is a forum that could advance reimbursement science and potentially help fill this vacuum.

The Green Park Collaborative

The Green Park Collaborative is a multi-stakeholder forum to advance regulatory science through clarification of the evidence expectations of public and private payers. It incorporates both patient and clinician perspectives and allows for participation by regulators and experts in methodology and clinical and life sciences. The Collaborative produces recommendations for study designs for specific clinical conditions, classes of interventions or methods and focuses on comparative effectiveness and value. Recent work includes the development of a guidance to compare sequences of therapy in advanced cancer with a focus on patient-important outcomes, including quality of life and time and cost burden. The Collaborative also

convened a workshop on evidence for weight loss interventions and produced a guidance on the clinical utility of next generation sequencing in clinical oncology.

Example: Guidance for late-phase drug studies of type 2 diabetes

A recent workgroup within this programme has focused on providing guidelines for late-phase drug studies of type-2 diabetes. Its emphasis has been on ensuring the studies will provide real-world evidence on patient-important outcomes and burdens and that the perspectives of patients, payers, clinicians and other stakeholders will be considered in any study design. These guidelines are needed, as whilst there have been hundreds of reported studies on diabetes treatments, these reports have offered few conclusions about effectiveness and real world safety. These deficiencies may be because of a lack of consistency in study design or limitations in trial outcomes, population, interventions and comparisons and study settings. The ten recommendations provided in this Effectiveness Guidance Document are organised in the categories of population, outcomes, methods and reporting for patient stakeholders (Figure 21).

Sustained dialogue on evidence, methods and standards for reimbursement are required to foster consistent expectations for product developers, improve reimbursement decision-making, achieve better balance of social objectives in tension and ultimately, to improve health outcomes

Sustained dialogue on evidence, methods and standards for reimbursement are required to foster consistent expectations for product developers, improve reimbursement decision-making, achieve better balance of social objectives in tension and ultimately, to improve health outcomes.

Population

1. Because racial and ethnic minorities and older adults are affected more by diabetes, but not enough is known about treatment effects in these groups, studies need to make every effort to include African-American and Hispanic patients and patients age 65 and older.
2. Because diabetes patients with other medical conditions are often excluded from studies, which makes it difficult to know how treatments will affect these patients, patients should not be excluded just because they have cardiovascular disease, depression, a history of cancer, mild cognitive impairment, or diabetes complications,
3. Because scientists are able to draw much stronger conclusions when they can combine the data from different studies, studies should report age, race, weight, and other characteristics of study participants in standard ways so results from studies can be combined.

Outcomes

4. Because quality of life is an important factor for patients evaluating treatments studies should include quality of life measures, specifically the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) and the Diabetes Treatment Satisfaction Questionnaire before treatment and after one year of treatment.
5. Because patients report they find treatment effects on weight extremely important studies should report more information about treatment effects on weight, including how many patients lost or gained 5%, 5% to 10% and more than 10% of their body weight.

Methods

6. Because adherence is often problematic for diabetes treatments, yet many studies do not report it, studies should report adherence at month 3 and 12 of treatment to capture both early and persistent adherence.
7. Because lifestyle factors such as diet and exercise can have a real impact on treatment effects and are usually recommended to patients yet not administered or reported in a standard way, all studies should include standard lifestyle counselling (on weight and exercise, as recommended by the ADA) for all patients
8. Because comparing new diabetes treatments with established ones provides much more useful information for patients, clinicians, and insurance plans than comparison with placebo or no treatment, studies should compare new treatments with alternative treatments rather than with placebo or no treatment.

Reporting

9. Because "real-world" aspects of a treatment affect the burden on patients and how likely they are to take medication as instructed, studies should report the requirements for storage, preparation, administration, supplies, devices, and doctor's and lab visits for each treatment they include.
10. Because study results are usually presented in very technical language in professional journals and patients participating in studies usually do not receive these results, the sponsors or authors of studies should create a layperson's summary of published results and make it available to study participants and the general public.

Figure 21. The Green Park Collaborative issued ten recommendations as part of its Effective Guidance Document for type 2 diabetes.

How can companies identify the evidence needed to support the value proposition

in product development

Prof Finn Børlum Kristensen, *Head of Coordinating Secretariat of EUnetHTA, Danish Health and Medicines Authority, Denmark*

Joint Action 2 (JA2) is the three-year programme (2010-2012) of the European Network for Health Technology Assessment (EUnetHTA). In JA2, the forty-nine partner organisation designated by the Ministry of Health, plus a large number of regional agencies and non-profit organisations that produce or contribute to HTA aim to bring "collaboration to a higher level resulting in better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the EU."

EUnetHTA developed the HTA Core Model, a framework for combined production and sharing of HTA information. This model consists of a set of generic questions that define the contents of an assessment, guidance for answering the questions and a common reporting structure. The nine domains or dimensions of value of the Core Model are used for full health technology assessments and the first four domains can be utilised for "rapid relative effectiveness assessments" (Figure 22).

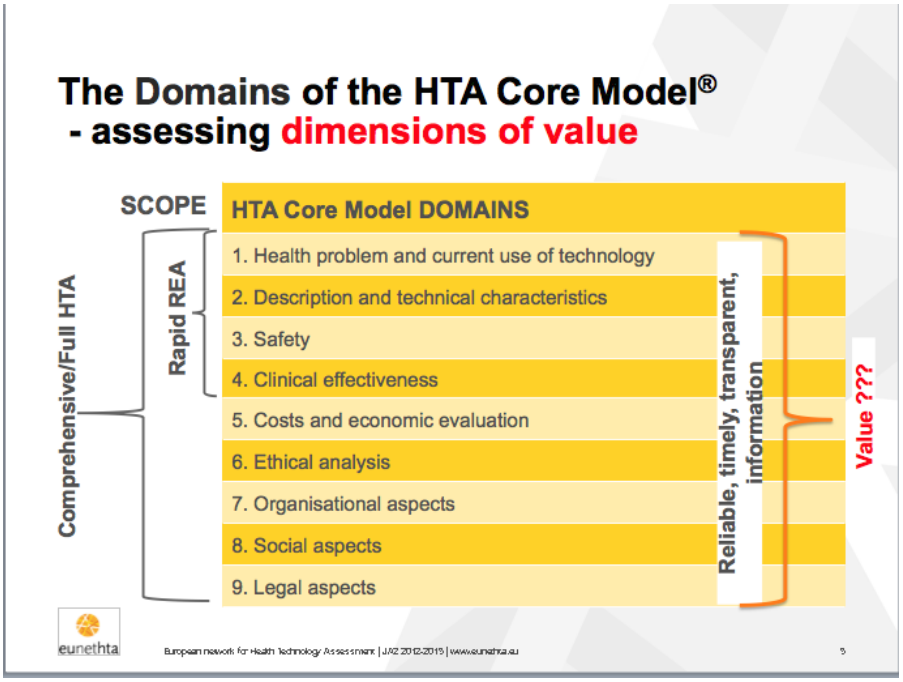

Figure 22. The domains of the European Network for Health Technology Assessment HTA Core Model.

Early dialogue

Early dialogue is the possibility for the sponsor of a new medicine or device to present the development plan for that product, ask questions about the planned studies and receive answers in the form of non-binding

scientific advice. Early dialogue has been available from regulatory agencies for the past fifteen years but only more recently from HTA agencies.

Potential questions can centre on the design of a clinical trial, including duration and dosing, endpoints and statistical analysis. Questions can also concentrate on economic data for populations, comparators, models, utilities values and resource utilisation. Sponsors have three options in seeking HTA advice in Europe, advice from a national HTA body, advice from the European Medicines Agency and some HTA bodies on both regulatory and HTA issues and cooperative advice from EU national HTA bodies for projects supported by the European Commission.

Participation in this programme of cooperative advice is voluntary among the HTA bodies. Co-funded by the European Commission there is no fee for companies and consensus among the HTA agencies for the nonbinding, prospective, confidential advice is achieved whenever possible. The company provides a structured submission file, or briefing book containing the development strategy, cost-effectiveness models and planned studies, prospective questions and company's position for each question relevant to the development plan. Questions are selected by the company at its own discretion and can relate to issues related to the relative effectiveness and/or economic aspects.

EUnetHTA Early Dialogues

Coordinated and hosted by the French Haute Autorité de Santé (HAS), twelve HTA bodies and nine companies participated in ten pilots (two preparatory) in 2012-2013 for ten medicines in various therapeutic areas. The EMA was invited as an observer in these one-day, face-to-face meetings. A survey was conducted among participants in this successful programme and allowed the development of a refined advice procedure.

Shaping European Early Dialogues

Also coordinated by HAS, Shaping European Early Dialogues for health technologies (SEED) is an international consortium of fourteen EUnetHTA partners, funded by the European Union in the frame of the EU Health Programme (2008-2013). SEED was developed to build on the EUnetHTA Early Dialogues experience and the ultimate objective was the development of two draft methodological protocols for early dialogues for drugs and medical devices. At the time of this Workshop, ten early dialogues for drugs and for medical devices or diagnostics/procedures were planned; seven multi-HTA early dialogues (four for drugs and three for devices) and three multi-HTA early dialogues with the EMA for drugs only. One early dialogue per month was planned to take place between May 2014 and February-March 2015, with feedback from all participants and a proposal for a permanent model for early dialogue in Europe to be submitted for comment to EUnetHTA and the HTA Network. Regulators, payers, patient representatives were invited to participate as observers in this programme.

Exchanges among HTA bodies will include an electronic meeting to identify the need for additional information or clarification in the briefing book and the exchange of written draft positions from each HTA agency. Followed by

- A pre-Sponsor meeting among HTA agencies to discuss divergent views
- The meeting with the Sponsor company to discuss key issues, with the minutes produced by the company and reviewed by HTA participants
- A post-Sponsor meeting among HTA agencies to make conclusions and proposals for further improvements

AS one outcome of this process, participating agencies in the SEED programme have initiated the development of recommendations for initial evidence generation for health technologies used to treat osteoarthritis of the hip and knee, including, diagnostic criteria, current treatments, study design, endpoints for symptom-modifying and disease-modifying technologies and economic assessment.

Moving forward

For synergies to be developed between the regulation and health technology assessment of medicines, a clear division of work and understanding of differences is required. The objectives of the regulation of medicine are the availability of high-quality, safe and efficacious medicines and the safety, performance, risk classification and clinical evaluation of devices; whereas the objectives of health technology assessment are the independent, objective and transparent collection of information to inform policy on health technologies.

Europe now has an official HTA Network Strategy and EUnetHTA has issued recommendations on the implementation of the scientific work and expects to continue delivering value through network alliances. At HTA 2.0 in Europe in 2014, it was agreed that network collaborations have created value for participants, that positive national results of European cooperation have been demonstrated and that national synergies between policy making, HTA and regulation have materialised at the EU level, getting effective technologies faster to patients.

. . . positive national results of European cooperation have been demonstrated and that national synergies between policy making, HTA and regulation have materialised at the EU level, getting effective technologies faster to patients.

Parent Project Muscular Dystrophy: A parent-led fight to end Duchenne Muscular Dystrophy

Patricia Furlong, *Founding President and CEO, Parent Project Muscular Dystrophy, USA*

Duchenne muscular dystrophy (DMD) is a rare, progressive and fatal disease caused by the absence of the structural muscle protein dystrophin. DMD is typically diagnosed in children between the ages of four to six and results in a gradual loss of muscle function and death when the patient is in his twenties. DMD occurs spontaneously in approximately 30% of cases.

When Ms Furlong started the Parent Project Muscular Dystrophy (PPMD) in 1994, DMD was largely unknown and there was no standard of care, clinical infrastructure, advocacy or education. As a result of the lobbying efforts of PPMD, the Muscular Dystrophy Care Act was signed into law in 2001 and brought in much needed funding for DMD research. There is currently a rich pipeline of drugs at various stages of development to treat DMD through dystrophin rescue or replacement or to treat muscle mass inflammation and fibrosis and cardiac issues and to impact the regulation of calcium. However, it is estimated that a lifetime of these therapies could cost three quarters of one million dollars per patient. In order to improve the existing structure and decision-making processes of regulatory and reimbursement organisations and expedite access to potentially important therapies, the PPMD has engaged in multiple advocacy activities.

In 2013, The PPMD published a white paper, *Putting Patients First: Policies to Promote Responsible Access to New Therapies,* which contained the policy statement drafted by the PPMD Board of Directors regarding its goals for the US Food and Drug Administration (FDA) that included recommendations to expand the use of accelerated approval for therapies intended to treat rare diseases, including DMD; issue clear guidance about the level of evidence required for the use of surrogate endpoints in order to expand the scope of acceptable endpoints; pilot the use of adaptive approval for serious and life-threatening disorders and give greater weight to the demonstrated benefit-risk preferences of patients.

[PPMD recommendations to the US FDA included that to] pilot the use of adaptive approval for serious and life-threatening disorders and give greater weight to the demonstrated benefit-risk preferences of patients

Because DMD was not among the twenty patient workshops planned by the FDA as part of its Patient-Focussed-Drug Development programme and in order to provide helpful data to better inform the FDA regarding the benefit-risk preferences of the DMD community, PPMD developed the PPMD Benefit-Risk Study, thereby converting the patient voice into acceptable data. The objective of the study was to explore how parents and guardians of individuals with DMD prioritise risk and benefit in the context of new therapies. Its specific aims were to describe risk tolerance, health-related quality of life and numeracy; explore treatment preferences, risk tolerance and benefit priorities; evaluate the effect of a child's disorder progression on treatment preferences and explore Duchenne-related worries.

The study employed the use of best-worst scaling in which the value a respondent derives from an object compared with a comparator is proportional to how often the respondent chooses it in preference to the comparator (Figure 23). Contributed by parents and refined by researchers, the “worry” domains in the study were child focused, including health, quality of life and social support and external to the child, including parent/guardian quality of life, social support and family effects. Similarly, a list of potential treatment attributes were contributed by parents and refined by researchers to be sufficiently balanced to allow a successful experiment. After a successful pilot, the final survey was implemented online and included questions on treatments, worries, risk-taking measures, numeracy, health-related quality of life, child’s DMD status, care and support items and demographics. Parents or guardians of at least one living child with Duchenne muscular dystrophy, living in the United States, over 18 years of age and able to complete an online survey in English were recruited from PPMD and the DuchenneConnect Registry.

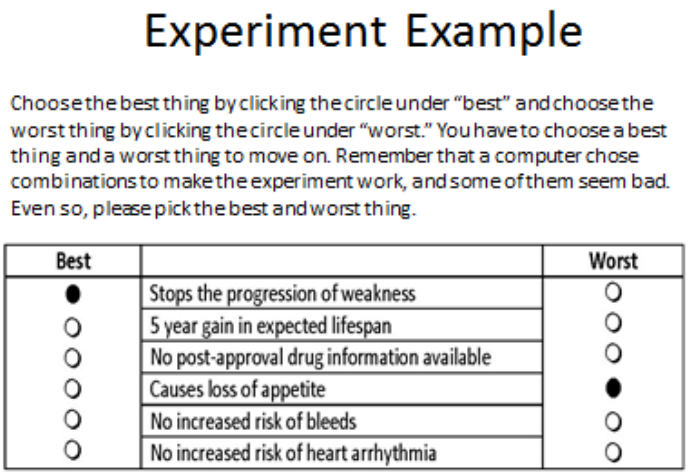

Figure 23. Best-worst scaling in the PPMD Benefit-Risk Study.

There were 119 parents who completed the survey with a mean age of 44 years and a mean age for their affected child of 12 years The majority of participants were Caucasian (92%), married (90%) earned more than $50,000 per year (84%) and had attained undergraduate, graduate or professional degrees (68%); had one affected child (92%); had private insurance (85%); and had participated in clinical research (58%).

Preliminary conclusions from the study include the fact that participants prioritised protection of muscle function over any other attribute, including longer lifespan and each of two serious risks (Figure 24) and their most significant worries were related to the child’s illness progression and care (Figure 25). The study suggests a parent population that is highly concerned about the effect of DMD on their child’s strength and is willing to accept risk and uncertainty for a treatment that would slow or stop muscle weakness. Survey results were presented to the FDA and discussions to expand the results of the survey are ongoing.

Finally, the PPMD developed a draft guidance to industry for developing drugs to treat DMD through the use of a Steering Committee, working groups, an Advisory Committee and a professional writer. At the time of this

Attribute description	Rank	Utility Score	Std Dev	Std Error	T-test	P-Value
Stops progression of weakness	1	0.88	0.337	0.01	69.44	0.0000
Slows progression of weakness	2	0.80	0.400	0.02	53.36	0.0000
Does not change progression of weakness	11	-0.08	0.514	0.02	-4.15	0.0000
5 year gain in expected lifespan	3	0.46	0.545	0.02	22.74	0.0000
2 year gain in expected lifespan	4	0.41	0.514	0.02	21.19	0.0000
No extra gain in expected lifespan	12	-0.11	0.367	0.01	-8.27	0.0000
2 years of post-approval drug info available	5	0.06	0.496	0.02	3.02	0.0013
1 years of post-approval drug info available	6	0.02	0.182	0.01	3.29	0.0005
No post-approval drug info available	9	-0.02	0.368	0.01	-1.52	0.0637
No increased chance of nausea	7	-0.01	0.251	0.01	-1.04	0.1483
Causes loss of apetite	13	-0.13	0.342	0.01	-10.27	0.0000
Causes loss of appetite with occasional vomiting	16	-0.28	0.500	0.02	-14.98	0.0000
No increased risk of bleeds	8	-0.01	0.140	0.01	-2.14	0.0160
Increased risk of bleeding gums and increased bruising	15	-0.27	0.442	0.02	-16.08	0.0000
Increased risk of hemorrhagic stroke and lifelong disability	17	-0.72	0.449	0.02	-42.81	0.0000
No increased risk of heart arrhythmia	10	-0.04	0.225	0.01	-4.50	0.0000
Increased risk of harmless heart arrhythmia	14	-0.17	0.379	0.01	-11.941	0.0000
Increased risk of dangerous heart arrhythmia and sudden death	18	-0.79	0.41	0.02	-51.13	0.0000

Figure 24. Ranking of therapy attributes in the PPMD Benefit-Risk Study

WORRY PRELIMINARY RESULTS	Utility score
My child getting weaker	-0.637
Getting the right care for my child over time	-0.254
My child missing out on new treatments	-0.245
My child feeling happy	-0.161
Managing my uncertainty about my child's future	-0.127
Affording care my child needs within the family budget	-0.065
My child having good friends	-0.038
My child not being able to express deep worries	-0.025
Being a good enough parent for my child	-0.012
The wellbeing of my other children	0.038
Me handling the emotional demands of Duchenne	0.049
My child feeling like a burden on the family	0.179
Effects of Duchenne on my closest relationships	0.217
My child becoming independent from me over time	0.232
Feeling isolated from other families	0.300
Having time for myself	0.557

Figure 25. Utility scores for worries in the PPMD Benefit-Risk Study.

Workshop the guidance had been submitted to the FDA and elements of this document were later incorporated into draft guidance released by the FDA 9 June 2015. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf) This guidance has potential impact on all future submissions and reviews of Duchenne candidate treatments and the PPMD draft ensured that patient and parent insight and data were contributed to FDA deliberations and is being viewed as a model and precedent for shaping the future by other advocacy groups for rare diseases.

Working toward value-based healthcare
A payer's (provider's) perspective

Rosmin Esmail, *Director, SCN Health Technology Assessment and Adoption, Alberta Health Services, Canada*

AHS Health Technology Assessment and Innovation

Formed in 2009, Alberta Health Services (AHS) serves a population of 4.1 million. Knowledge management and translation within the Health Technology and Assessment and Innovation Unit of AHS acknowledges that the success of evidence-informed decision-making depends on the understanding and dissemination of the principles of HTA across AHS. Activities within four functional areas are used in the management and translation of knowledge across the organisation (Figure 26).

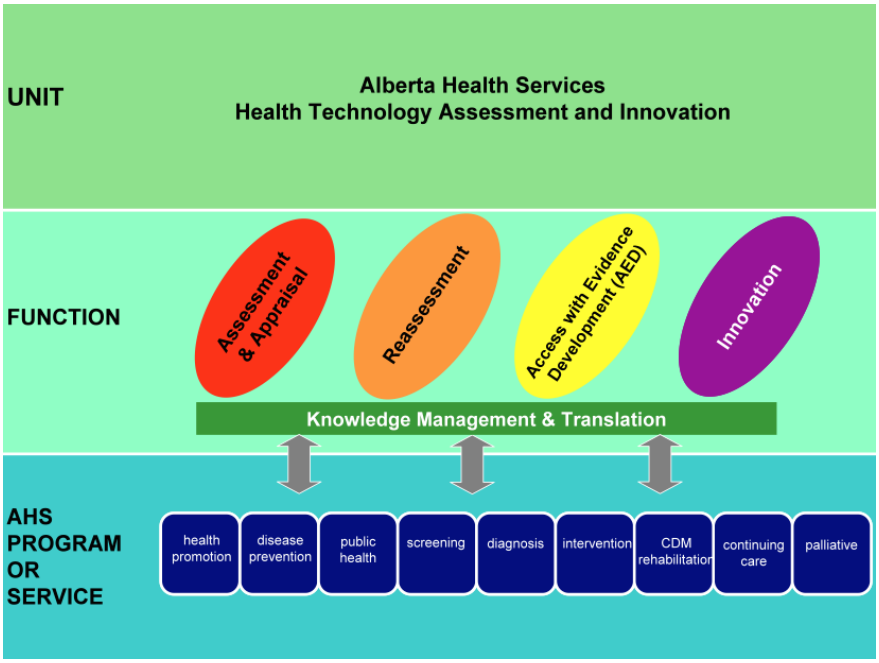

Figure 26. A schematic representation of the role of the Alberta Health Services (AHS) Health Technology Assessment and Innovation unit in managing the transfer of knowledge across the health services in Alberta.

Through its ***assessment and appraisal*** function, the unit reviews and makes recommendations on health technologies through the systematic evaluation of global literature with respect to the clinical and economic properties, effects and direct and indirect impacts of emerging health technology, applying this evidence to the AHS context. Programmes within this function also identify and prioritise emerging health technologies and coordinate outcomes monitoring and reporting. Through its ***reassessment*** function, the unit leads proactive re-assessments of potentially obsolete and/or (cost-) ineffective technologies that may be superseded by safer, more (cost-) effective technologies or those deemed to provide little health gain for the cost. Potential recommendations arising from these assessments might include disinvestment or the removal or reduced use of the technology; substitution with innovation, that is, the better use of existing technology. Through its ***access with evidence development*** function, the unit designs and conducts field evaluations, including

pilots and trials to collect AHS-specific data on effectiveness and cost effectiveness of new technologies in early stages of technology development to reduce uncertainty of adoption in the province. Through its ***innovation*** function, the unit supports innovations developed within and outside AHS in the areas of clinical testing, validation, data collection and value proposition within the framework of AHS priorities and needs.

Perspectives on value

The value proposition for new health technologies can be considered from the different levels within the structure of healthcare in Alberta. The macro level is represented by the payer, the Alberta Ministry of Health, the mezzo layer is represented by the provider, Alberta Health Services and the micro level is represented by the AHS Strategic Clinical Networks.

As detailed by Henshall and colleagues at the HTA Policy Forum, in their efforts to allocate resources to technologies of proven value, providers generally rely on a wide range of evidence and a wide range of views on value and on appropriate assessment and may frequently seek advice from expert committees or bodies, clinical experts, patients and patient organisations while also trying to balance patients' views with those of the wider public and balance the value gained by new technologies against the values lost through opportunity costs. Providers may also need to take account of political or commercial considerations when decisions become the focus of public attention. The provider also needs to determine the unmet clinical needs, as well as the clinical and economic value and benefits a new technology will bring to the patient, the payer, or society.

Using the principles of timeliness, rigour, transparency and flexibility, the Alberta Health Technologies decision process selects health technologies and services for provincial review, conducts health technology assessments of selected health technologies and services, consults on findings, formulates advice, communicates decisions and evaluates the impact of those decisions. The Alberta Advisory Committee on Health Technologies advises Alberta Health on decisions requiring provincial review and makes policy recommendations. Screening subcommittees review technologies submitted for consideration by the decision process using criteria that include population-wide impact, anticipated requirement for change in legislation, anticipated change in access or unequal access among health sectors, significant impact on health or quality of life, cost, impact on fee schedule, impact on cost allocation between Alberta Health and Alberta Health Services, significant potential investment in Alberta and controversy or political sensitivity.

At the micro level, Strategic Clinical Networks are collaborative clinical strategy groups charged with incorporating the perspectives of all stakeholders, developing improvement strategies and achieving improvements in patient outcomes and satisfaction and access to healthcare and sustainability. SCNs have been established in many therapeutic areas including diabetes, obesity and nutrition; seniors' health, bone and joint health; cardiovascular and stroke; cancer and addiction and mental health. AHS supports SCNs through the evidence synthesis of rapid and scoping reviews, full systematic reviews and health technology assessments, health economics advice, health technology assessment and reassessment support, linkage with Alberta Health and policy decisions and the tracking and horizon scanning of technology trends.

In 2014, the Canadian Network for Environmental Scanning in Health (CNESH) evaluated information on a number of new and emerging technologies and developed a watch list that included antimicrobial copper surfaces to reduce hospital acquired infection, ex-vivo lung perfusion device to preserve donor lungs, ipilimumab treatment for metastatic melanoma, a mitral valve clip for degenerative mitral regurgitation and obinutuzumab for chronic lymphocytic leukaemia.

Future opportunities and challenges

Any regulatory and reimbursement decision-making process needs to ensure that both value and the value proposition are defined from the provider perspective and that these values are considered at the macro, mezzo and micro levels. There is also a need for a framework for the early interaction and collaboration between technology assessment agencies and industry in the development and evaluation of new medicines.

Any regulatory and reimbursement decision-making process needs to ensure both value and the value proposition are defined from provider perspective and that these values are considered at the macro, mezzo and micro levels.

A regulatory perspective on value

Barbara J Sabourin, *Therapeutic Products Directorate,*

Health Products and Food Branch, Health Canada

A country of approximately 37 million people, Canada has the eighth largest pharmaceutical market in the world and is the seventh fastest growing global market. Pharmaceuticals are an important component of healthcare in Canada and represent 16% (the second largest component) of total Canadian health expenditures.[1] Although brand-name products account for 76% of Canadian pharmaceutical sales, generics are a rapidly growing market. From 2001 to 2012, pharmaceutical exports and imports between Canada and the rest of the world have increased by 136 percent and 93 percent respectively. More than half of Canadian pharmaceutical production is exported, primarily to the United States and a significant portion of the Canadian market is supplied by foreign imports from the United States and European Union**.**

The healthcare responsibilities in Canada are split between different levels of government with the federal level responsible for regulation of products and the provincial, or territorial, level responsible for delivering healthcare services and regulating healthcare professions. The Health Products and Food Branch (HPFB) takes an integrated approach to managing the health-related risks and benefits of health products and food. It does so by minimising health risk factors to Canadians while maximising safety via the regulatory system, by promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Canada is now a member of the Steering Committee of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) and is involved in several other international initiatives with organisations such as the International Coalition of Medicines Regulatory Authorities (ICMRA), International Pharmaceutical Regulators Forum (IPRF), Asia Pacific Economic Cooperation (APEC), Pan American Health Organization (PAHO), Pan American Network for Drug Regulatory Harmonization (PANDRH). In addition, the agency has memoranda of confidentiality with many jurisdictions, which allows information sharing and the discussion of challenging regulatory issues. User fees allow many Health Canada activities to be completely or partially cost recovered.

During the review process Health Canada considers information provided by the sponsor through dossier submission regarding the efficacy of a new product; that is “substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended.” That evidence could include pivotal clinical studies, possibly also “supportive” clinical studies and phase I data. Information is also evaluated for the safety of the product; that is, “detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended.” That evidence could include all

relevant clinical studies, all relevant non-clinical data, phase I data and post-marketing data if available. Information outside the submitted dossier may also be considered such as expert advice, medical literature, treatment guidelines and information from other regulatory bodies.

The value proposition for Health Canada

Health Canada employs a regulatory system based on the determination of quality, efficacy and safety throughout a product life cycle. The agency performs clinical trial assessments, its market authorisation requirements are similar to other jurisdictions and requirements are in place for compliance with Good Manufacturing Practices. Health Canada monitors signal assessments leading to updated safety information and as well as product recalls and suspensions and it provides accurate, timely benefit-risk information to facilitate decision making, not only through product monographs and prescribing labels but through a series of vehicles such as health risk communications, healthcare professional letters and other information updates.

The regulatory system has changed in response to stakeholder needs and there are now a variety of available regulatory pathways that provide flexibility such as priority, notice of compliance with conditions, extraordinary use new drugs, generics and orphan drugs. Health Canada can provide expertise as needed related to developing issues such as pandemic flu, severe acute respiratory syndrome (SARS) or Ebola and it is now authorised to ensure that sponsors fulfil the terms specified in notices of approval with conditions. There is increasing interaction between Health Canada and Canada's health technology agency, the Canadian Agency for Drugs and Technologies in Health (CADTH). This interaction includes pre-submission, pipeline and product monograph finalisation meetings with industry; Scientific Advisory Committee Meetings and meetings of the Drug Safety and Effectiveness Network. In addition, Health Canada attends the annual CADTH Annual Symposium.

[Health Canada] has changed in response to stakeholder needs and there are now a variety of available regulatory pathways that provide flexibility . . .

Evaluation processes and practices continue to evolve for Health Canada as they do for regulatory and HTA agencies globally, toward a system of evidence-based decisions, transparency and cooperation among partners and a lack of duplication. The goal of this evolution is timely access to safe and effective therapeutic products.

Reference

1. IMS Institute for Healthcare Informatics. *Pharmafocus 2017; 2013.*

APPENDIX: WORKSHOP ATTENDEES

Regulatory and government agencies	
Prof Hans-Georg Eichler	European Medicines Agency
Rosmin Esmail	Alberta Health Services, Canada
Dr Don Juzwishin	Director HTA and Innovation. Alberta Health Services, Canada
Prof Finn Børlum Kristensen	Danish Health and Medicines Authority, Denmark
Barbara Sabourin	Health Canada
Barbara Walman	BC Ministry of Health, Canada
Health technology assessment agencies	
Dr Nicholas Crabb	National Institute for Health and Care Excellence, UK
Frank Gavin	Canadian Agency for Drugs and Technologies in Health
Niklas Hedberg	the Dental and Pharmaceutical Benefits Agency (TLV), Sweden
Prof Robert Peterson	Canadian Institute of Health Research
Dr Chander Sehgal	Canadian Agency for Drugs and Technologies in Health
Academic institutions	
Prof Bruno Flamion	University of Namur, Belgium
Prof Lou Garrison	University of Washington, USA
Dr Anke Hövels	Utrecht University, The Netherlands
Patient groups and non-profit organisations	
Patricia Furlong	Parent Project Muscular Dystrophy, USA
Dr Sanjay Gupta	Daiichi Sankyo Inc, USA
Dr Katharina Kovacs Burns	Best Medicines Coalition, Canada
Dr Donna Messner	Center for Medical Technology Policy (CMTP), USA
John Sproule	Institute of Health Economics, Canada
Lona Vincent	Michael J. Fox Foundation, USA
Pharmaceutical companies	
Dr Katja Berg	Sanofi, UK
Frank DeFelice	Merck, Canada
Dr Ka Lum	Genentech Inc, USA
Dr James Murray	Eli Lilly and Company, USA
Dr Ludwig Steindl	Bayer Pharma AG, Germany
Koen Torfs	Janssen NV, Belgium
Wan Tsong	Eisai Inc, USA
Rebecca Yu	Janssen, Canada
Gergana Zlateva	Pfizer Inc, USA

Centre for Innovation in Regulatory Science	
Nicola Allen	*Research Fellow*
Patricia Connelly	*Manager, Communications*
Lawrence Liberti	*Executive Director*
Dr Neil McAuslane	*Director*
Professor Stuart Walker	*Founder*
Tina Wang	*Portfolio Manager, HTA Programme*