HTAi Conference, Vancouver, June 2018
Strengthening the Evidence-to-Action Connection

Panel Session Report

HTA, From Reacting to Innovation to Proactively Involved in Technology Development. Lessons Learnt and Ways Forward

Key points

- Patients believe that all stakeholders should proactively contribute to value-based research, which considers the end-game (HTA), reduces the innovation gap and brings better treatments to patients faster.
- Industry values EUnetHTA Early Dialogues but consistent high quality needs to be assured, with a consolidated report of convergent and divergent views to inform evidence generation plans.
- EUnetHTA continues to proactively develop a suite of approaches with stakeholders and partners to influence evidence generation plans over the life cycle of the technology to produce data relevant for HTA and reduce uncertainties.
- The CADTH Scientific Advice Program uses a flexible process that provides specific advice to influence evidence generation plans and the overall process can identify advances in technologies and analytical methods for which CADTH should prepare.
- New investments in Canada will help build capacity for the regulator (Health Canada), CADTH and other partners to work together to influence evidence generation plans.

- All stakeholders are keen to take a more proactive approach to understanding what is needed to demonstrate value and reduce uncertainties to enable faster access to health technologies that demonstrate added value.
- A new paradigm is needed that encourages very early dialogue with all stakeholders (particularly payers, clinicians and patients) before technologies are chosen for development (mode 2.0).
- There is potential for global collaboration within companies, across HTA bodies, regulators, patient organisations and collaborative initiatives to advise on evidence generation plans by continuing to develop dialogues and mechanisms for post launch evidence generation.

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About HTAi

Health Technology Assessment international (HTAi) is the global scientific and professional society for all those who produce, use, or encounter HTA. HTAi has members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. HTAi is the neutral forum for collaboration and the sharing of leading information and expertise. This panel was judged by three reviewers and selected for presentation at the 2018 annual meeting by the International Scientific Program Committee.

Status of this report

This report has been prepared by an independent consultant, Karen Facey and approved by presenters to become a public record of the HTAi panel session.

It should be cited as:
Granados A, Low E, Meyer F, Mujoomdar M, Bettle M. *HTA, From Reacting to Innovation to Proactively Involved in Technology Development. Lessons Learnt and Ways Forward.* Report of HTAi 2018 Panel Session. Health Technology Assessment International – Canada. 2018.

Funding

Karen Facey received a fee from Sanofi Genzyme to help organise this panel session and write this report.

HTA, From Reacting to Innovation to Proactively Involved in Technology Development. Lessons Learnt and Ways Forward

1. Introduction and Industry Perspective

Dr Alicia Granados, Head Global Health Technology Assessment Scientific Strategy, Sanofi Genzyme

As moderator, Dr Granados introduced the rationale for the panel. Health Technology Assessment (HTA) is continuously evolving. At the outset HTA mainly informed policy makers about “big ticket” technologies. Now HTA is taking a more proactive role, advising on the development of new health technologies, rather than simply reacting to innovation when it arrives to be assessed. It has developed interactions with stakeholders (industry, clinicians, regulators etc) to facilitate multi-stakeholder dialogues and support health technology management. More recently, there has been increasing involvement of patients in these processes.

These dialogues (known as Early Dialogue, Scientific Advice, Scientific Consultations or Early Advice) are one of the most innovative approaches, not only in HTA, but also in healthcare. As experience has been gained with them, their benefit has been observed at several points in the life cycle of the health technology.

The aim of new approaches to HTA is to enable patients earlier access to the right innovative technologies by improving technology research and development plans, HTA processes, value alignment and healthcare prioritization, making them more effective and efficient. This panel brings together a range of stakeholders to reflect on how HTA has evolved from taking a reactive approach to simply assessing innovation when it arrives to being more proactive, focussing particularly on the dialogues.

Giving an industry perspective, Dr Granados reflected on the lessons learnt after engaging in the EUnetHTA Early Dialogue processes.

The EUnetHTA Early Dialogues have provided:

- ✓ an opportunity to align internal strategies on evidence generation plans
- ✓ a test of whether proposed evidence generation plans are relevant for different health authorities and patients
- ✓ a transparent & constructive discussion with stakeholders on the target value proposition
- ✓ input to the internal Go/No Go decision making process
- ✓ opportunity to educate HTA bodies on disease and product specificities
- ✓ a chance to provide feedback on HTA processes and stakeholder engagement.

Compared with the longer-established regulatory scientific advice process, there are still some challenges in HTA dialogue processes as shown in Table 1.

Table 1. Learnings from EUnetHTA Early Dialogue Processes

Issue	Proposed solution
Some HTA bodies prepare and participate less fully in the process	Good coordination among regulatory and HTA bodies and moderator has a high level of scientific expertise
Patients are involved too late	Involve patients from the beginning to the end of the process
Healthcare professionals are not consistently involved	Involve healthcare professionals to help all stakeholders understand the course of the disease
The report is not always clear and specific and so cannot be used to drive evidence generation plans	The report should present the convergences of opinions across countries, areas where there are divergent opinions and the specific issues raised by individual HTA bodies
Dialogue over the whole life cycle of the technology is not possible	“Continuous dialogue” over the life cycle of the technology would be helpful to discuss issues such as use of real world evidence

These challenges can be solved if we leverage HTA competencies and develop the leadership skills of those coordinating the dialogues.

2. Patients' Perspectives

Eric Low OBE, Chairman, the Amyloidosis Research Consortium UK
Past Chief Executive, Myeloma UK
Independent Consultant

Mr Low shared his perspective as someone who has been involved in patient advocacy for over 20 years. Reflecting on the need to be proactive vs reactive is particularly interesting at this time, as there appears to be a perfect storm brewing, as described in Figure 1. The environment is complex, with many issues that impact HTA, from both the supply (industry) and the demand (health system/patient) side. In such a complex setting, it is imperative that all stakeholders work together to weather the storm by finding win-win solutions as well as identifying opportunities that lay ahead.

Figure 1. The Perfect Storm Brewing for HTA

To set the scene, this is about dealing with allocation of scarce resources. There is not enough money to do all the things that everyone would like to do in healthcare. There are tensions in the system. On the one side are society/patients/clinicians who demand more and suppliers who could be perceived as trying to maximize shareholder value. On the other side, payers are trying to manage budgets. HTA is in the centre of this. So, there is an opportunity to create HTA 2.0, which uses its unique position to resolve the disconnects that currently exist between supply and demand.

Over the past twenty years, as a leader of a patient organisation for myeloma, I have experienced these disconnects first hand in many HTAs at NICE in England and the SMC in Scotland. When a medicine comes to market it is like a square peg trying to fit into a round hole. NICE and SMC do not make a negative recommendation because there is a lack of patient involvement, but rather because there is too much uncertainty relative to the price of the medicine, so it is a risk to invest and there is an opportunity cost (other patients elsewhere in the healthcare system would lose out).

The question is how to increase certainty in HTA and create a stronger value proposition so that more health technologies are approved for the benefit of patients. As it takes a long time to develop a medicine, there are lots of opportunities along the way to think about value-based research that seeks to demonstrate a strong value proposition with reduced uncertainties. The best way to achieve this is through early dialogues, being much more proactive about how medicines are brought to market, not just reactive. So, unlike the perception of stakeholders in the past, HTA can be part of the solution, not the problem.

Another issue from patients' perspectives, is that considering the level of investment that goes into all types of research, the actual benefit that patients get is completely disproportionate. Great progress has been made, but it could be so much better and more efficient, if the way in which research was undertaken was rethought. Through better prioritization mechanisms, use of disease specific blueprints, early dialogues, making better go/no go decisions and thinking about the systems approach, more could be gained from the major investment that is made into medicine development. This "innovation gap"[1] between our rapidly increasing understanding of disease and the actual benefits achieved by patients from new treatments needs to be reduced.

As HTA has been moved closer to the point of marketing authorisation, there has been some acceptance that HTA will not have the evidence it requires. So, alternative mechanisms to support access have been found, such as confidential discounts (in Managed Entry Agreements or Patient Access Schemes) to bring cost effectiveness below acceptable willingness to pay thresholds as well as to address uncertainties. This is not a sustainable business model and it does not mean that patients get the best possible treatment. It simply means the budget is managed. It does not consider patient outcomes.

To bring more value to the market, processes need to be altered to start with the end in mind. Health systems' and patients' needs must be identified and fed back into health technology development pipelines to reduce the innovation gap. This is strategic evidence development. It seeks to resolve the disconnect between the evidence required by regulators and HTA and ensure that clinicians and patients make good decisions about investments, treatment and care.

Confirmatory studies designed primarily for regulatory purposes need to be the best they can be and reduce the uncertainty seen in HTA by careful consideration of their design, comparators, confounding factors, endpoints etc. Furthermore, industry often funds investigator led studies in academia, but these rarely contribute to explaining the value propostion or reducing the uncertainties in HTA. There is an opportunity for industry to work with academia to develop "hybrid studies", which produce additional real world data that can mitigate risks and data uncertainties. This could also help medicine optimization, to determine the best way to use a medicine in clinical practice.

The life cycle model is essential to ensure that the right medicines are given to the right patients at the right time, that industry can get a return on investment and that the health system budget is managed and buys high quality outcomes for patients.

There are many timepoints along a technology life cycle that could benefit from stakeholder involvement and dialogues. Although patient experts are sometimes included in these discussions, patient advice is often ignored and involvement is tokenistic.

[1] Barker R. Bioscience: Lost In Translation – How Precision Medicine Closes the Innovation Gap. Oxford. 2016.

An example of a patient group being proactive, not reactive, is in relation to the NICE appraisal of bortezimib in 2005. Myeloma UK had assumed that as the medicine had received a marketing authorisation and it was in an area of such high unmet need, it would receive a positive recommendation from NICE, but it did not. After initial shock, Myeloma UK, reviewed NICE's appraisal and agreed with them. The evidence was insufficient. However, Myeloma UK did not want this to happen again and so was proactive. They setup an academic clinical trial network in the UK to work with industry and share the burden of evidence generation. The aim was to think strategically about how uncertainties in a confirmatory regulatory study could be mitigated. The Myeloma UK Clinical Trial Network developed several phase IIb studies that they took to NICE scientific advice in partnership with companies who presented their plans for confirmatory study(ies). NICE was asked to review the studies side by side, recognising that the confirmatory study had gaps for an English HTA, but presenting the phase IIb study as a potential solution to fill those gaps.

In addition to this collaborative research, Myeloma UK did its own research to generate evidence about patient benefit that would not be part of clinical development plans, covering the areas shown in Table 2.

Table 2. Other Evidence to Demonstrate Value

Type of evidence	Value for HTA/Payers
Localized epidemiological data, by disease stage and type	Help payers understand the budget impacts of new therapies
Current care patterns and associated outcomes across geographies and clinically important sub-populations	Inform relevant reference groups for health economic evaluations of new therapies
Quantitative descriptions of disease progression, associations between short-term changes (as may be observed in clinical trials) and long-term outcomes	Extrapolation/modeling of lifetime impacts required by payers
Patient and caregiver utilities/values, quality of life, comparative effectiveness with standard of care, societal benefit, real world relevant populations etc	Help payers understand the value proposition of new therapies; and influence development and choice of patient relevant outcomes/future research decisions

The question remains about how to combine the evidence coming from a variety of sources into a value-based research strategy that builds the value proposition throughout clinical development. Delloite (Davis et al. 2017)[2] has proposed a new end to end evidence management framework flowing from discovering value, generating value to optimizing value in research, clinical development and commercialization. This includes elements such as biomarker validation, clinical trial optimization, comparative effectiveness research and strategies for market access. They note that success with such evidence life cycle management will require increased transparency, advanced analytics and linkages between disparate data types.

The challenge this panel needs to address is how can we develop a systems model where we move from generating evidence for a regulator to value-based research, reducing the innovation gap and improving patient outcomes.

[2] Davis B, Morgan J, Shah S. Getting real with real-world evidence. Delloite Development LLC. https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-ls-2017-real-world-evidence-survey-031617.pdf Accessed 16 July 2018.

3. EUnetHTA Early Dialogues and Beyond: A Lifecycle Approach to Evidence Generation

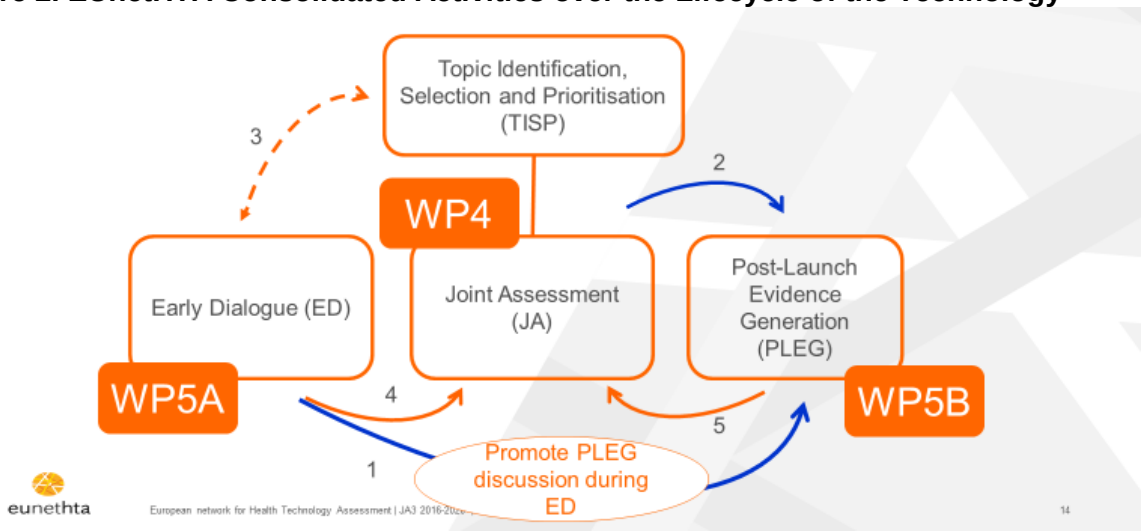
François Meyer MD, Haute Autorité de Santé (HAS)
EUnetHTA Work Package 5 Lead Partner

Dr Meyer gave an overview of the work of the European Network for HTA (EUnetHTA), which has been in operation for over 10 years and seeks to be proactive.

EUnetHTA involves 38 HTA organisations in 22 Member States across the European Union in a voluntary cooperation. It has been partly funded by the European Commission (EC) and HTA bodies through Project and Joint Action grants. EUnetHTA is currently in its third Joint Action of Member States (JA3) and covers a four-year period until 2020. It is not a legal entity and so cannot impose actions on partners. The future beyond JA3 will depend on the EC proposal to develop a permanent and sustainable network for HTA cooperation across Europe.

It is essential to see EUnetHTA as a consolidated set of activities, not as isolated WPs, otherwise efficiency is undermined. Figure 2 outlines the work of EUnetHTA Work Package 5 (WP5) that addresses evidence generation to suit the needs of HTA. Its main objective is to help generate optimal and robust evidence for different stakeholders along the entire life cycle of a technology, to bring benefits for patient access and public health. WP5A is co-led by HAS and G-BA to implement Early Dialogues about evidence generation plans at an early stage in the life cycle of a technology. Later in the life cycle, WP4 undertakes joint/collaborative assessments of a health technology and at this time WP5B considers the need for Post-Launch Evidence Generation (PLEG) to enable reassessment of the health technology at a later stage.

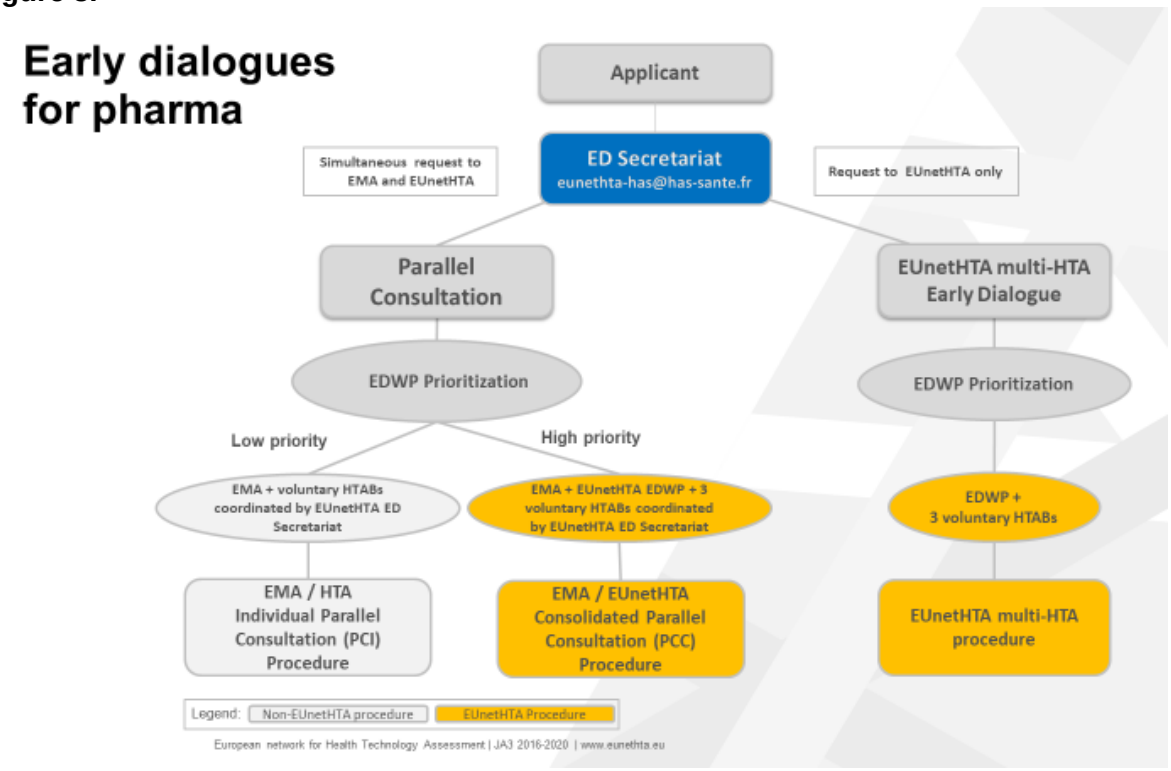
Figure 2. EUnetHTA Consolidated Activities over the Lifecycle of the Technology



WP5A: Early Dialogues

WP5A has learnt from the previous dialogue processes in single, multi-HTA and parallel HTA/regulatory Scientific Advice and Early Dialogue processes (Granados et al. 2016)[3] and has listened to feedback from stakeholders, particularly industry to develop its new processes as shown in Figure 3.

Figure 3.



For pharmaceuticals, the new Early Dialogue processes offer:

- flexibility to choose either multi-HTA or parallel consultation with regulators
- a more consistent approach, through establishment of the Early Dialogue Working Party (EDWP), with members from selected HTA bodies[4] to identify members that have the capacity and capability to contribute
- a scientific coordinator and rapporteur for each high priority multi-HTA and parallel Early Dialogue to produce a *consolidated* report presenting areas of agreement and issues specific to individual HTA bodies. HAS has been scientific coordinator of the first five Early Dialogues with G-BA acting as rapporteur. There will be a rotation of responsibilities in Q3 2018.

To date there have been 33 requests for Early Dialogues of medicines across a range of therapeutic areas. Of these, 13 have proceeded to the new consolidated process for either multi-HTA or parallel Early Dialogue. Up to the end of May 2018, seven consolidated reports had been completed. Sixteen requests have proceeded to individual parallel consultations

[3] Granados A, Mullin T, Moseley J, Meyer F, Avetisyan R, Wong-Rieger D, Kaatee M, Skinner M, Leyden S. *Multi-stakeholder Approaches to Improve Evidence-Based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations.* Report of HTAi 2016 Panel Session. Health Technology Assessment International – Canada. 2016.

[4] HAS, G-BA, NICE, AIFA with RER, NIPN, ZIN with RIZIV/INAMI

with EMA that are facilitated by EUnetHTA, but which do not have the same level of consolidation. Four requests were not taken forward.

Medical devices have not previously been able to access Early Dialogues and so new procedures have been developed for them that build on the experience with medicines, including:

- templates to support development of a good Briefing Book
- selection criteria to choose medical devices for the Early Dialogue process.

This will be piloted on two medical devices in Q3 2018.

Patient involvement is also important to EUnetHTA, but limited resources must be managed, so a range of approaches is being tested, as outlined in Table 3. Patients' contributions will be taken into account and to ensure transparency the involvement will be documented in the report and feedback taken to understand the impact of each approach.

Table 3. Testing Various Approaches in Patient Involvement in EUnetHTA

Approach	Patient contribution deliverables	Patient time	Use to date
Interview individual patients (living with the condition) in local language collecting general feedback on the disease + answers to specific questions related to the dossier (In at least 2 countries)	• Minutes of interviews in annex • Documentation of patient contribution in final EUnetHTA recommendations • Feedback questionnaire	~2 days of work	5 EDs including interviews with individual patients (France, UK, Spain)
Interview national patient representative (living with the condition/care-giver) in local language collecting general feedback on the disease + patient representative position on applicant dossier	• Minutes of the interview in annex • Documentation of patient contribution in final EUnetHTA recommendations • Feedback questionnaire	~5 days of work	7 EDs with interviews of a German patient representative
Participation of EU patient representative (living with the condition/care-giver) in the overall ED process including interview with coordinator, multi-stakeholder face-to-face meeting, review final recommendation	• Minutes of the interview in annex • Review final EUnetHTA recommendations • Feedback questionnaire	~7 days of work	3 EDs with an EU patient representative participating in the overall ED process

In 2019, Early Dialogues will be developed in WP5A by:

- considering the addition of Norway/Sweden and Spain to the EDWP
- implementation of new tools
  - for the Secretariat to manage the high number of requests
  - to train "new" participants from HTA bodies, especially those doing Scientific Coordination and Rapporteur roles for the first time
- stabilizing the rotation schedule for Scientific Coordination responsibilities
- conducting first non-pharma Early Dialogues
- discussing involvement of healthcare professionals
- establishing a new financing mechanism.

WP5B: Post-Launch Evidence Generation

The other panellists have stressed the need for a life-cycle approach to evidence generation. This is at the heart of EUnetHTA JA3 and so WP5B will provide advice on Post-Launch Evidence Generation (PLEG). It will involve two main activities:

1. multi-stakeholder cross-border PLEG pilots for medicines and non-medicine technologies to confirm possible levels of collaboration and develop procedures
2. development of a tool for registers to improve the quality of PLEG in HTA.

The PLEG pilots:

- evaluate the evidence gaps
- agree the requirements for PLEG and define the research question
- consider how the data can be collected taking account of data sources in national settings (as EUnetHTA has no funds to finance the data collection itself)
- analyse the data.

PLEG candidates can be identified from EUnetHTA Joint Assessments in WP4 that identify evidence weaknesses relating to:

- populations
- comparators (or use of indirect comparisons)
- outcomes (overall survival, quality of life, patient satisfaction, serious adverse events)
- study design.

Two PLEG pilots are underway. One, on an orphan medicinal product started in April 2018 and is led by AIFA with seven partners. The other, on a medicine for breast cancer, started in May 2018 and is led by TLV. Each pilot is expected to end in mid-2019. A PLEG pilot on a medical device led by Avalia-T is yet to start.

Lessons are already being learned, particularly in terms of timing. As national bodies have their own processes for collecting or accessing health service data, these can take time to establish or organise (e.g. registries).

Strand WP5B is working with EMA to develop a disease specific approach to PLEG by improving registries. EUnetHTA has participated in the EMA procedure for “qualification” of two registries to ensure that they provide data of sufficient quality for HTA. This qualification process needs to be refined and consideration needs given to the process for reviewing existing registries. Furthermore, the EMA collaboration will not be appropriate for non-medicine technologies.

EUnetHTA is proactive and is asking industry to ensure that they give a <u>global commitment</u> to all EUnetHTA work to put individual products through the EUnetHTA life cycle process from Early Dialogue, to Joint Assessment and then PLEG. It is hoped that this will happen soon.

4. CADTH's Scientific Advice Program

Michelle Mujoomdar PhD. Director Scientific Affairs. CADTH.

Dr Mujoomdar reflected on the development of CADTH's Scientific Advice program, with additional insights gained from a recent secondment to EUnetHTA.

Despite the success of dialogues taking place in Europe, CADTH identified that there was still the disconnect Mr Low outlined in Canada, between the evidence that CADTH, payers and patients needed to make decisions and the design and results of the studies presented in HTA submissions. Frequently, gaps in evidence were identified in CADTH assessments, which could have been resolved with better evidence generation plans. Several stakeholders, particularly pharmaceutical companies, asked CADTH to develop a Scientific Advice program. This was launched in 2015 as a fee-for-service model, providing non-binding, confidential advice.

Being relatively new, the CADTH Scientific Advice process was able to learn from the other dialogue processes developed in Europe. Furthermore, given the small size of the program it has been possible to reflect on processes, adapt them and make them more flexible, which may be easier than in a multi-country initiative.

Figure 4 shows the standard timeline. From receipt of Briefing Book to the face-to-face Scientific Advice meeting is about 14 weeks and the record of the Scientific Advice is produced four weeks after that.

Figure 4. CADTH Scientific Advice Process

Like the rest of its processes, patient and clinical involvement is integral to CADTH Scientific Advice. Relevant clinical experts are included in the team for each Scientific Advice procedure. For each Advice procedure, one or two patients are interviewed and their views are presented in the Advice document. There is also an indication of whether patients' views align or conflict with the proposed development plan.

Unlike some other dialogue processes, CADTH provides its Advice to the company at the face-to-face meeting. It also aims to be flexible and can customize the process according to the company's needs. For example, the timeline can be shortened for smaller requests and companies may segment their advice meetings into specific parts at different times.

A range of activities is underway to develop the Scientific Advice program at CADTH:

- exploring opportunities to deliver Scientific Advice for medical devices
- developing multi-HTA Advice, perhaps with NICE, and other HTA organisations
- Parallel Scientific Advice with the Canadian regulator, Health Canada.

Reflecting on the development of dialogues in Europe and CADTH Scientific Advice:

- there is an opportunity to collaborate internationally to share experiences about implementation of dialogue processes
- there is a need to balance the form of advice with the resource available. It should be specific and actionable where possible, but it is resource intensive to produce such technical/detailed advice compared with strategic/broad advice
- if there is a sufficient volume of Advice procedures, there is “value-add” for an HTA body as they provide early intelligence about new types of technologies and methodological approaches that will be coming into HTA, which can help develop internal preparedness.

CADTH has a strong track record in HTA. Next year it will celebrate its 30th anniversary and can contribute a lot to HTA developments such as early dialogue processes. It is open to global collaboration to create multi-HTA advice for medicines and medical devices.

5. Early Scientific Advice at Health Canada

Megan Bettle PhD. Director, Regulatory Review of Drugs and Devices, Health Canada (National Regulator for Medicines and Devices)

Dr Bettle provided insights into the recent policy initiatives in Canada that are enabling Health Canada to develop a more proactive approach to improving access to medicines, in collaboration with its HTA partners and stakeholders.

In 2016, Canada approved 33 new medicines (new active substances). Over half of these medicines (60%) underwent an accelerated regulatory review (priority review or conditional authorization) and 15 were considered "orphan medicinal products" drugs by EMA or FDA. So, submissions for marketing authorizations are made to Canada for innovative medicines and some of these are for small populations. The median time to regulatory approval in Canada is similar or faster than other major regulators. However, as a recent CIRS report shows[5], many medicines are not submitted to Canada for authorization first. In 2016, 85% of the new active substances approved by Health Canada had already been approved by other regulators (generally FDA and EMA). The median gap between submissions to the first authority and to Canada was approximately 6 months.

Health Canada accepts pre-submission meetings with industry. These meetings are often used as opportunities to familiarise the regulatory reviewer with the phase III trials and the submission that is about to be made. They are rarely held early enough to influence the evidence generation plan for a product.

Companies can also ask Health Canada for advice on Phase I-III clinical trials that are to be conducted in Canada, before a clinical trial application is made. This advice is generally reactive – i.e. commenting on a trial proposal, rather than advice to support *de novo* trial planning. For smaller companies, advice on how to run appropriate research was given, but not what research was required.

As part of the Regulatory Review of Drugs and Devices (R2D2) initiative, a consultation was undertaken with pharmaceutical companies in late 2017 to ascertain if Early Advice (regulatory early dialogue) with Health Canada would be useful. The responses differed depending on sector but some thought that scientific advice could lead to more efficient regulatory reviews and higher quality submissions.

- Larger companies indicated that their focus is on requirements in larger markets (EMA/FDA).
- Generics companies stated scientific advice would be valuable as there are differences in comparators across countries.
- Companies with products that might qualify for accelerated review were much more interested in getting advice from Health Canada to understand how to design their studies.
- Advice given in parallel with HTA organizations was also seen as valuable by many stakeholders.

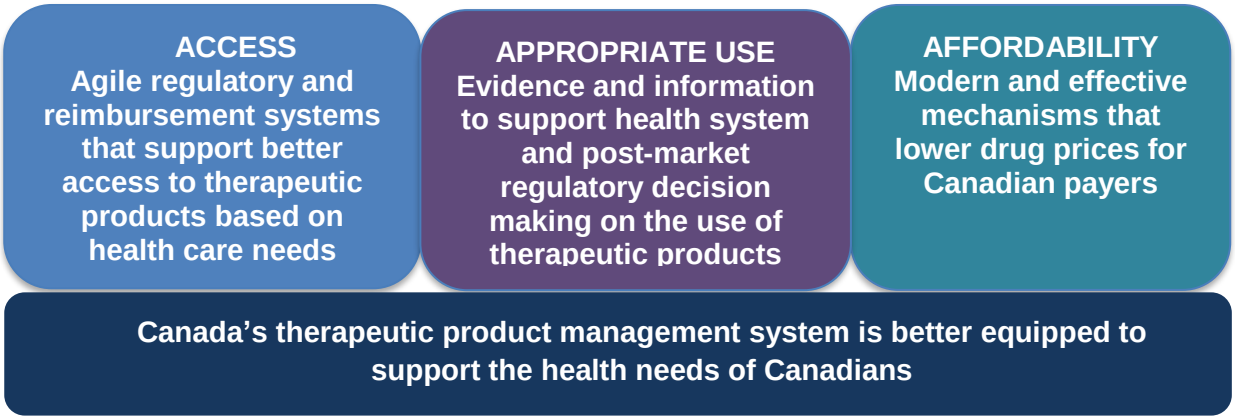
Prior to this, in 2015, Health Canada established a three-year pilot to provide scientific advice about the types of studies needed for biosimilars and to advise on the structure of the regulatory submission. Up to May 2018, no one had requested such advice. However, submissions for biosimilars have been made to Health Canada and they have been

[5] CIRS. New drug approvals in six major authorities 2007-2016. CIRS R&D Briefing 2017. http://www.cirsci.org/wp-content/uploads/2017/11/CIRS-RD-Briefing-65-20112017.pdf

approved without the advice. So, this demonstrates that it is not enough to just offer the advice service. It has to be the right advice about the right product.

The R2D2 project is a multi-year initiative that has received substantial funding to build capacity and review regulatory tools, structures, processes and regulations to streamline processes for products coming to market. It has been established to meet commitments made by the Federal and Provincial health ministers to approve access, affordability and appropriate use of therapeutic products as shown in Figure 5.

Figure 5. Regulatory Review of Drugs and Devices – Implications for Medicines



Health Canada, as the pharmaceutical regulator, is the first gatekeeper in the healthcare system. The R2D2 initiative has given it more resources to allow it to be proactive and enhance work with partners to help bring appropriate products to market. Part of this includes developing parallel scientific advice with our HTA partners.

There are practical challenges to doing this, as the regulatory and HTA operational processes are different. One example of this is that at CADTH, the staff who give the advice are not the same as those who assess the product. However, Health Canada uses those who have the subject matter expertise for both elements of advice and review. Health Canada also does not currently charge for provision of Early Advice, whereas CADTH does. Industry is also concerned that the delineation of mandates between HTA and regulation is maintained and that regulators do not stray into cost considerations.

However, all partners are solution driven and work is underway to map the CADTH and Health Canada approaches and consider how the two processes could be brought together. Parallel Scientific Advice pilots will be undertaken over the next year to draw out questions of interest to each stakeholder and consider how efficiencies can be gained. It is likely that the most value will be achieved in the life cycle approach, which will support health technology management. This may be particularly valuable for medicines for small populations or where there is accelerated approval and a need to generate real world evidence. In these situations, it will be particularly important to work with HTA partners to agree how the evidence development plan should be shaped.

Health Canada does hold some pre-clinical trial meetings for medical devices and pre-submission meetings for medical devices, but similar to medicines these tend to be late in development.

The R2D2 initiative covers medical devices, but the processes for medical devices are less well developed and manufacturers tend to be smaller and sometimes in need of additional advice. So, the aim is to be able to provide appropriate regulatory and parallel HTA scientific

advice for some medical devices. This will probably focus on the highest risk, most innovative devices (Class III and IV). There may also be the possibility of providing eLearning activities when it is not feasible to give face to face guidance.

Full details of all the plans, projects, timelines and consultations in the R2D2 initiative can be found on this webpage.
https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html

6. Discussion

Dr Granados reflected on the contributions from the panelists. There does seem to be a new paradigm emerging that is proactive. It could be termed as an “adaptive mindset”, where all stakeholders are adapting to each other’s needs in terms of research, assessment etc. An important invitation has also been made to develop international collaborations. This will not only influence the effectiveness of individual activities such as early dialogues but will ultimately impact the efficiency of the healthcare system. Another important thread running through all presentations is the need to ensure effective patient involvement so that the outcomes that matter to patients can drive effective research and understanding of patient benefit. This will this help industry do its research more effectively and HTA to understand added value.

By a show of hands approximately 10 of the 75 people in the audience indicated that they had been involved in early dialogues.

Dr Granados then asked the audience for their views on the panelists presentations.

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Dr Chris Henshall (HTA consultant, UK) - Thinking about Mr Low’s proposal for a new paradigm, for HTA 2.0. What is happening in Early Dialogues is amazing, but it seems to be improving the old paradigm, where industry produces technologies and then tries to find out if patients and clinicians want them and if they can get them reimbursed. How could we move to a new paradigm where we enable dialogue before this? Where companies say we have this idea for a product that we are thinking of spending a huge amount of money developing and before we do that we would like some views to help us prioritize our pipeline. I’d be very interested to hear the panels view on this, recognizing that there are questions subsequent to this, like who would be involved in such “Very Early Dialogues? Clinicians, patients and the healthcare system (payer), but perhaps not HTA, which has been setup to be reactive. So perhaps we should move more generically to mode 2.0?

EL – Improving what we already do is not a bad thing but I agree we need to move beyond this. Experience has shown that patient organisations can be seen as the honest broker. The starting point for the new paradigm is disease pathway modelling that captures what clinicians and patients think they need in 5 or 10 years from now and use that to drive innovation. The Ministry of Defence does not get people knocking on its door saying we have built this new helicopter, what do you think? The Ministry of Defence knows what it needs, they write a blueprint and issue a tender. That is how we get to mode 2.0. It is incumbent upon disease specific areas to work out what they need from a demand side and work with industry from a supply side to deliver. Otherwise it is still a supply driven model.

FM – Let us not forget that Early Dialogues are not that old, they are still innovative. However, thinking about "Very Early Dialogue": in the EMA pilots for adaptive pathways there was a safe harbour phase where companies could come at a very early stage, for informal advice. This provided the opportunity to have a preliminary discussion about whether the proposed medicine was likely to be of value or not. These adaptive pathway pilots have been stopped prematurely, so we have little experience of this approach. However, companies can present their portfolio of products to EMA and sometimes to HTA bodies. It is complementary to early dialogues and can help companies identify the main questions that might arise.

MM – HTA bodies differ. CADTH consider decision makers in Canada as its customers and seeks to identify what is important to them. CADTH is not meant to be a proxy for decision makers but it does try to stay connected and integrate the needs of the healthcare system into its work, for example in terms of defining its priority areas. In terms of very early dialogues about pipelines, many HTA bodies are open to this and its up to companies to engage. There is also information in the public domain about patient needs and the disconnect with research is fairly stark. This is shown by the work of the James Lind Alliance[6] that works with patients, carers and clinicians to agree which uncertainties about treatment effects (for any form of health intervention) matter most. In response to Dr Henshall I would say that you should not exclude HTA bodies from a new paradigm for very early dialogues, as HTA bodies try to keep abreast of the issues that are important to the health system.

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Dr John Gillespie (Medtronic Australia) – At an ICHOM (International Consortium for Health Outcome Measurement) conference a few years ago it was highlighted that industry needs to get patients and the healthcare system to discuss what is of value at the outset of their work. Reflecting on Mr Low's points about investigator-led studies, industry does focus on sales and it is often the clinician that makes the decision about whether to buy a product. As a consequence, trials are often undertaken to suit the needs of clinicians and they are often designed in the US, where there is much less experience of HTA. This means that it can be difficult to bring this evidence in to HTA. So, there does need to be a change in thinking at higher levels in industry. Furthermore, there is an opportunity for healthcare systems to use their own data better to identify the population's biggest needs. My question is how do we meet the needs of lots of different stakeholders across the evidence development continuum?

MM – There have been various international initiatives such as ICHOM, others include the Green Park Collaborative USA etc to involve different stakeholders in the development of core outcome sets, some using robust research mechanisms such as Delphi processes to develop consensus. Although some HTA bodies have participated in these initiatives, there is an outstanding question about how their outputs will be used in HTA.

FM – Approaches that enable collaborative working within disease areas and are not product specific are to be welcomed.

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[6] http://www.jla.nihr.ac.uk/about-the-james-lind-alliance/ Accessed 18 July 2018.

Unknown academic (Radboud University Medical Center, Netherlands). Working at a University Hospital, developers approach us with new ideas for health technologies and ask whether we think there is value in it. We have access to all stakeholders. Hence there is a role for academia to help determine the need for a new technology and to advise on the research needed to demonstrate value. How does the panel feel about the role of academia?

AG – When we talk about multi-stakeholder, we often talk about patient, clinician, regulatory, HTA, payer, developer. We need all kinds of experts that can add value to this process of dialogue and defining optimal evidence generation. Academia cannot be excluded and of course most clinicians involved in HTA have an academic link.

FM- The involvement of academia is necessary. However, EUnetHTA is a project with a limited budget and that relies on substantial contributions in kind. So, there is a limit to what can be achieved with the resources available. We are aware that engagement with academia needs to be developed and so a forum has been held with academia to discuss more involvement in future.

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Unknown man (Market Access Consultant, Canada). Question for Canadian panellists. The new aligned (regulatory and HTA) review process that reduces timelines to market access in Canada is very positive. However, at the same time the PMPRB (pricing regulator) and pCPA (coalition of Provinces that jointly negotiate prices for medicines) are extending their timelines. So, there is concern amongst industry about going through the new Canadian authorisation and appraisal processes and then not being able to negotiate a price. What is your view on these two instruments and whether they are obstructing a parallel (regulatory/HTA) process?

MB – The Canadian pricing regulator has recently proposed some changes to the regulation that would cap maximum prices. At the moment Health Canada is working on the upstream elements to bring together the regulatory and HTA assessments to overlap them as much as possible to compress timelines. There is collaboration with PMPRB and pCPA, but the latter is new and still developing its systems. We are particularly considering “what is a priority”? Health Canada has a Priority Review and CADTH has established a process to define priorities. We currently use the same words, but they mean different things. So, we need to think about how we prioritize and work together across the system. That will not occur for every medicine, but there are certain circumstances where there are shared priorities that everyone can work on. I cannot speak for the pricing authority, but those conversations about priorities are happening now in a way they never have before and that is promising.

MM – Upstream investment (for Scientific Advice) helps downstream. The challenges downstream at marketing authorization and HTA appraisal arise when there are major uncertainties. There are times when a product is assessed and it is obvious that the uncertainties could have been addressed with a better evidence development plan.

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Glossary

AIFA	Agenzia Italiana del Farmaco (Italy)
CIRS	The Centre for Innovation in Regulatory Science
EDWP	Early Dialogue Working Party
EMA	European Medicines Agency (regulator)
EUnetHTA	European network for HTA
FDA	Food and Drug Administration (US regulator)
G-BA	Gemeinsame Bundesausschuss (Germany)
HAS	Haute Autorité Sante (France)
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
ICHOM	International Consortium for Health Outcome Measurement
JA	Joint Action
NICE	National Institute for Health and Care Excellence (England/Wales)
NIPN	National Institute of Pharmacy and Nutrition (Hungary)
pCPA	pan-Canadian Pharmaceutical Alliance
PLEG	Post-Licensing Evidence Generation
PMPRB	Patented Medicines Pricing Review Board
R2D2	Regulatory Review of Drugs and Devices (Canada)
RER	Regione Emilia-Romagna
RIZIV/INAMI	RijksInstituut voor Ziekte- en InvaliditeitsVerzekering/ Institut National d'Assurance Maladie-Invalidité
SMC	Scottish Medicines Consortium
TLV	Tandvårds-Läkemedelförmånsverket (Sweden)
WP	Work Package
ZIN	Zorginstituut Nederland