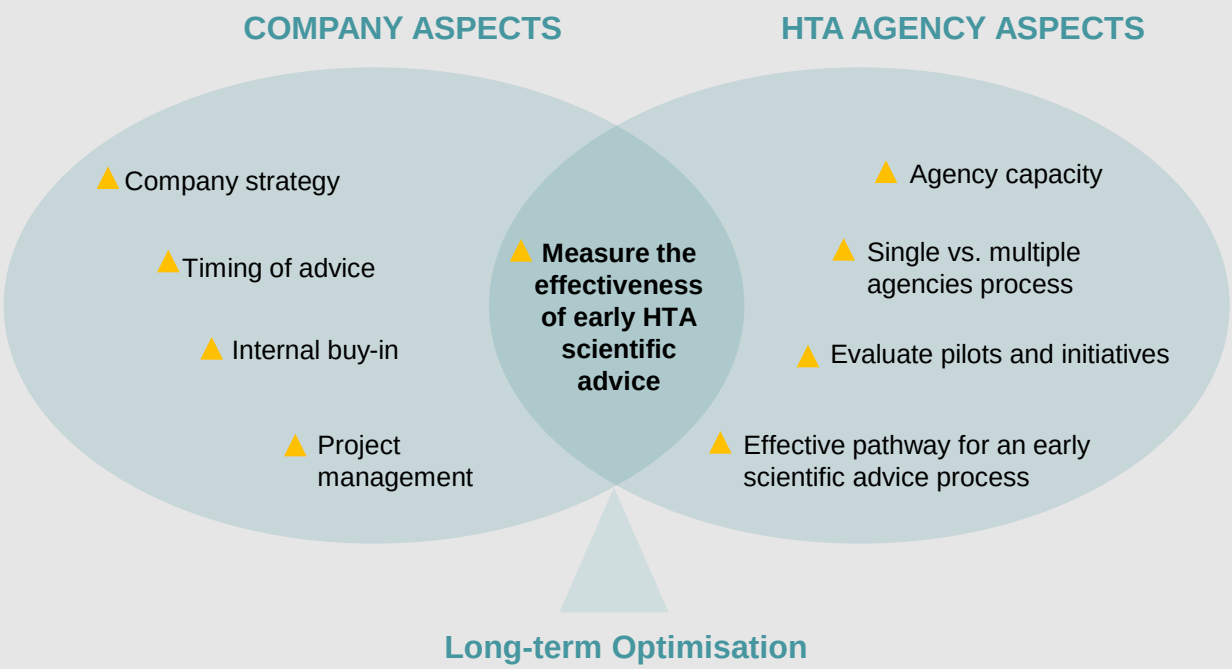
Early scientific advice from HTA agencies:

How does the effective use of the various kinds of advice support a positive HTA recommendation?

Highlights from a Technical Forum convened by the Centre for Innovation in Regulatory Science (CIRS); 11 December 2015, Heathrow, UK

Summary of key points from CIRS Technical Forum on early HTA scientific advice



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CIRS Centre for Innovation in Regulatory Science

R&D Briefing 60

Report prepared by

Tina Wang, MSc, Manager, HTA Programme
Neil McAuslane, PhD, Director
Lawrence Liberti, MSc, RPh, RAC, Executive Director
Patricia Connelly, BA, ELS, Manager, Communications

About CIRS

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 EC1N 8JS UK

Email: cirs@cirsci.org
Website: www.cirsci.org

Forum background

For some time, pharmaceutical companies have sought scientific advice from regulatory agencies to improve the efficiency of their studies, enable better trial design and support the goals of their regulatory submission. These same companies have now initiated efforts to incorporate the requirements of health technology assessors and payers into drug development programmes and early scientific advice from health technology assessment (HTA) agencies is increasingly being used to ensure an effective, efficient and coordinated development programme. Challenges have emerged, however, that include international variability in processes and divergent methodologies and requirements, creating a complex and challenging environment in which industry must determine the best pathway for obtaining and using HTA agency advice.

Pilot studies for joint regulatory and HTA agency advice are now ongoing, as well as those for advice from multiple HTA agencies. The goals of these studies are the alignment of procedures and technical requirements; it remains to be determined, however, how the use of these various kinds of scientific advice supports access success.

The Centre for Innovation in Regulatory Science (CIRS) activities in early HTA scientific advice began in 2009 with the conduct of a stakeholder survey to inform the CIRS Workshop *Review and Reimbursement: A special case for better co-operation* and continue through current research, international Workshops, industry and agency discussion meetings and technical fora.

CIRS recently conducted a focus survey among its members to explore the perceptions and experiences of companies seeking HTA scientific advice.

A CIRS Technical Forum held in December 2015 addressed the key learnings and implications of the survey and included discussions of optimal approaches to seeking and implementing early HTA advice to accelerate access to new medicines.

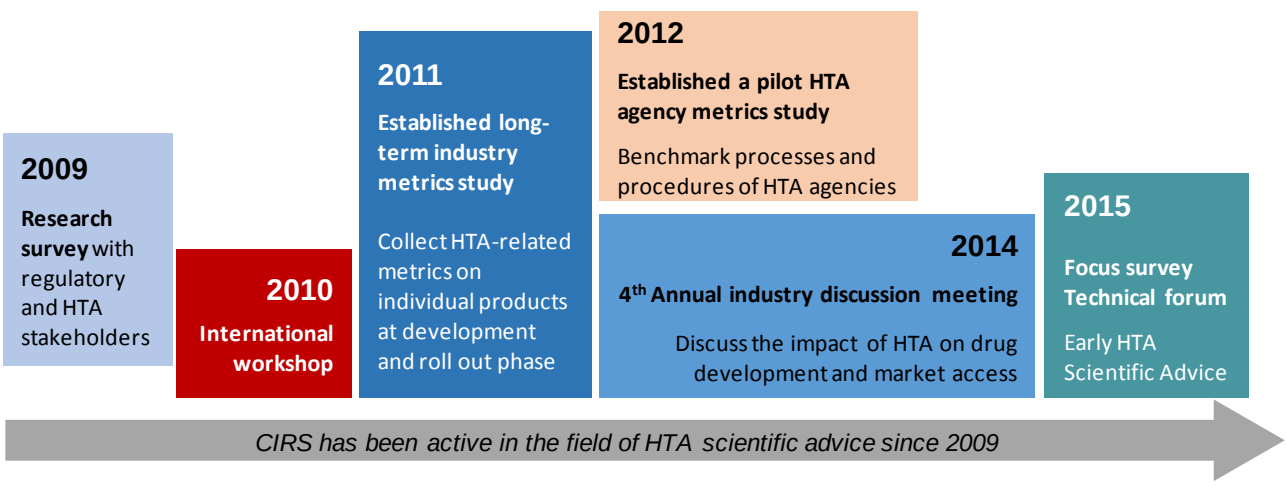
This R&D Briefing 60 summarises highlight from the Technical Forum convened by CIRS on 11 December 2015, Heathrow, UK

Forum objectives

- ✓ Identify companies' current approaches to seeking early scientific advice by discussing the outcome of the CIRS industry survey on the perception of and strategies for HTA consultations, and to discuss how this industry experience can support evidence generation and jurisdictional submissions
- ✓ Improve the understanding of the current initiatives of multi-stakeholder consultations to identify learnings and challenges posed by these pilots and to address the implications of using the pilots to achieve greater alignment of evidentiary requirements
- ✓ Discuss the optimal pathway of early HTA advice in terms of when, on what topics, and from whom to seek advice and how processes can be improved to increase the efficient use of resources

Companies participating in the Forum

- Actelion Pharmaceuticals Ltd, Switzerland
- Astellas, The Netherlands
- Bayer AG, Germany
- Biogen, UK
- Eisai Pharmaceuticals, UK
- Eli Lilly and Company, UK
- GlaxoSmithKline, UK
- Janssen Pharmaceutica NV, Belgium
- Pfizer, UK
- Roche, Switzerland
- Sanofi, France
- UCB Biopharma, UK



Forum highlights: Strategic approach for obtaining HTA advice

Meeting participants discussed the strategic approach for obtaining HTA advice. Four potential steps were suggested.

1. Move to a systematic consideration of seeking HTA advice

- Establish a formal governance committee that specifies the criteria for seeking HTA advice and the processes that should be followed
- Build internal company capacity and expertise to prepare for, attend and benefit from these meetings
- Communicate understanding of business priorities for products and value of HTA advice to all internal stakeholders

2. Select a meeting time based on the objectives

PHASE I	EARLY PHASE II	BEYOND LATE PHASE II
To resolve uncertainties in a new therapeutic area where science is still evolving and where there may be no existing guidelines	For technical issues such as guidance on study design or economic modelling	Confirmation of study design; determination of local study comparators; phase IV planning

3. Select a meeting format by balancing advantages and drawbacks

	Single HTA agency advice	Multiple HTA agencies advice	Parallel regulatory and HTA advice
ADVANTAGES	Agency can comment on comparator choice relevant to national healthcare system and standard of care	Increased probability of alignment and cohesive viewpoints	Early identification of divergence between regulatory and HTA evidence requirements
DRAWBACKS	Time consuming to conduct individual meetings with all key HTA agencies; diverse advice	Complex logistics including timing, language and attendees	Resource intensive; potential focus on regulatory issues

4. Maximise long-term value of seeking HTA advice

- Tell HTA agencies which advice will be taken up and which will not be possible to include in a development programme
- Assemble a database of accrued information on scientific advice from HTA agencies as a knowledge resource
- Develop methods of disseminating the learned expertise internally such as through workshops

Forum highlights: Problems and solutions for seeking HTA advice

Meeting participants talked about the problems of initiating and seeking HTA advice and discussed potential solutions.

	PROBLEMS	SOLUTIONS
Company strategy	There is a lack of understanding among companies' clinical development teams regarding the value of early advice and evidence of the value of advice is only now starting to accrue.	Collect metrics on individual products that provide insights into the value of integrating HTA-related requirements into development programmes.
Optimise the value of HTA advice	Internal teams may discount the value of HTA advice because of its sometimes divergent nature and resulting additional development requirements.	Companies have databases of collected regulatory learnings and feedback and should consider the compilation of similar repositories of accrued information on HTA-related scientific advice as well other methods of disseminating expertise and experience such as workshops.
Internal buy-in	Internal teams may be unwilling to delay research programmes to wait for the outcome of an HTA advice meeting.	Early understanding of business priorities for the company such as intended jurisdictional rollout timing is critical, as scientific advice strategy will flow from those priorities.
Timing	The available time and resources of the global or operating companies to assemble briefing documents is typically the rate-limiting factor in submissions.	With their established project management system and medical writing support to prepare briefing documents and established management systems to archive previous submissions and advice procedures, company regulatory teams can be a significant resource.
Project management	Project management, particularly timeline management, presents challenges to the receipt and implementation of early scientific advice	The preparation of a guidance document on how best to interact with HTA can help build interest from and alignment across company stakeholders.
Agency capacity	Many agencies have limited resources. Because of a heightened interest in scientific advice, scheduling advice meetings has become increasingly challenging.	Frequently-asked-questions-and-answers documents would help to ensure that advice sessions focus on questions that are of the greatest value to all stakeholders. Agencies could also consider responding to written questions to reduce the number and duration of face-to-face meetings. Performing triage via teleconference or prior written submissions for individual points of clarification might also improve review timelines and allow a better focus for the face-to-face interaction.

Forum session 1: How are companies currently using scientific advice? Learnings and challenges

Forum programme

- Outcome of the 2015 Focus Survey: Companies' current strategies and perceptions of seeking HTA advice – **Tina Wang,** *Manager, HTA Programme, CIRS*
- Company viewpoint : Use by teams to inform drug development plans – **Deven Chauhan,** *Senior Director, Value Evidence Leader, GSK*
- Company viewpoint : Use by management in go/no go decisions – **Dr Jens Grueger,** *Head Global Pricing & Market Access, Roche*
- Roundtable discussion: Incorporating HTA advice into the decision process

Scientific advice strategy

Rather than using an established process for seeking HTA advice, most companies participating in the survey only routinely seek advice for high-priority products or for those in new therapeutic areas or with uncertain evidence.

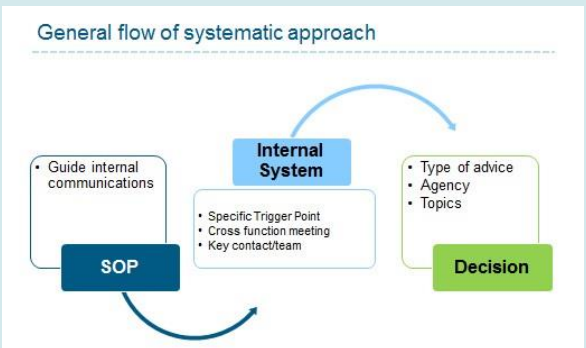
"Very few companies that participated in the CIRS survey had a strategy for seeking early HTA scientific advice for every new development programme. For most cases, this strategy is developed on a case-by-case basis."

Tina Wang

However, once it was determined that scientific advice would be solicited for a product, the majority of participating companies either had or were developing a process that specified from whom, when and on what topics that advice would be sought. In addition, one Forum participant explained that the late-stage portfolio at his company then routinely used the advice as part of the decision-making process.

Recommendation

Industry should move from a case-by-case to a more systematic consideration of HTA advice.



From the 2015 CIRS Focus study: an illustration of a systematic approach to seek scientific advice.

When to seek scientific advice

"Although it has been the position of some companies that national HTA or joint scientific advice is best targeted after phase III, others feel that early engagement is critical, particularly for technical issues such as guidance on study design or economic modelling."

Deven Chauhan

Most CIRS survey participants indicated that they first seek HTA advice during phase II development. This is in comparison to the results of a 2009 CIRS survey that showed that only 8% of responding companies sought HTA advice during phase II. However, it was also remarked during the Forum that product development teams should consider HTA requirements when building a product profile and that late phase II may be too late to make any needed major changes to a development plan.

Despite the recognised value of early HTA advice, as was brought out in Forum discussions, identifying an HTA stakeholder with the experience and expertise to offer needed advice early in development presents a particular challenge. In any case, the majority of companies in the CIRS survey seek HTA scientific advice at multiple time points in product development and this advice can yield an ongoing benefit.

"Even if the phase III programme has been finalised, advice can still help to fine-tune an integrated evidence plan (real-world, modelling, phase IIIb/IV)"

Jens Grueger

Although many aspects of HTA advice are beginning to be considered on a par with regulatory advice in influencing industry decision making, there is one exception.

"Whilst regulatory advice formally affects the assessment of the future value of a product; that is, products typically are rated with a regulatory probability of success based on historic experience; consideration of 'access probability of success' has not generally been quantified because of insufficient experience and fast-changing, unpredictable local access environments."

Jens Grueger

Forum session 1: How are companies currently using scientific advice? Learnings and challenges

Internal challenges for using HTA Advice
Development teams trying to obtain and incorporate HTA advice into product plans are often confronted with internal barriers.

Excerpts from Roundtable discussions

- Many internal stakeholders are not aware of the value of early scientific advice for the company and communicating that value is a significant challenge because the concrete results of the benefits of advice are only starting to become available.
- Although companies are largely receptive to the advice, competing priorities within the organisations and protocol review committees can create a gap between the receipt of the advice and a decision as to whether or how to proceed with implementing the advice in product development.
- Project management, particularly timeline management, presents challenges to the receipt and implementation of early scientific advice. It was suggested that commercially led teams may be more systematic in their approach and that in decentralised companies, procedures can vary among business units and countries.
- Resources devoted to early scientific dialogue varied greatly and the process is not part of the project management system in some companies and may be supported through the budgets of varying teams or departments, with medical writing and other responsibilities outsourced.

Suggestions to overcome these barriers also emerged during Roundtable discussions.

Recommendations

- Set appropriate incentives for implementation of early scientific advice within companies by establishing buy-in at a high-level.
- Use regulatory team experience and resources to understand how to capture learnings from early HTA scientific advice and schedule and monitor the outcomes of scientific advice, interact at advice meetings and use medical writing support to prepare briefing books.
- Establish early understanding of company business priorities such as intended product rollout timing to obviate pushback from colleagues who may not be prepared to wait for needed advice.
- Consider the rotation of regulatory colleagues into market access roles and vice versa to widen perceptions and understanding regarding the value of HTA-related scientific advice.

From the presentation of Deven Chauhan: Ways industry can optimise HTA scientific advice.

Choosing the format for advice
Forum participants discussed the pros and cons of advice from single HTA agencies, multiple HTA agencies and parallel HTA-regulatory advice.

- Whilst advice from a single HTA agency may result in a locally relevant developmental programme, it is time consuming to acquire results from all necessary individual agencies and this advice may be diverse and difficult to prioritise or align.
- Although parallel regulatory-HTA advice may result in early alignment of the product profile, a disproportionate amount of time may by spent on regulatory issues in advice sessions.
- Despite potentially complex logistics and intensive use of resources, a multi-HTA strategy was considered optimal because all the invited HTA bodies would have met for discussion beforehand and although there may be disparities, there is an increased probability of alignment and a cohesive viewpoint.

Recommendation

Consider a multi-HTA strategy for the increased probability of alignment and a cohesive viewpoint.

Challenges to the multi-HTA strategy include the need to invite participants from multiple affiliates and to determine questions that will yield the most relevant advice. Whilst it is vital to have the right participants to move discussion forward, too many participants limit the ability to obtain and process feedback.

Recommendations

- Use a decision tree to decide which questions to be asked and stakeholders to engage in multi-HTA advice consultations.
- Ensure that participants in advice consultations have decision-making capabilities.

Forum session 2: How can we measure the success of a scientific advice meeting? Which is the optimal pathway?

Forum programme

- Outcome of the 2015 Focus Survey: Is the multi-stakeholder scientific advice meeting the most effective way to achieve alignment of evidentiary requirements? – **Dr Neil McAuslane**, *Director, CIRS*
- Company viewpoint: Analysis of four early dialogues as part of the Shaping European Early Dialogues (SEED pilot: Lessons learned and way forward **Anouchka Vidal,** *Market Access Payer Engagement, Sanofi* and **Marie-Laure Prudhomme,** *Market Access Payer Policy, Sanofi,*
- Roundtable discussion : What is the most effective pathway of scientific advice?

Case study

Sanofi shared their experience in the recent early dialogue meetings as part of SEED pilot to solicit advice for a chronic disease therapy (one with phase IIa evidence and one with phase IIb evidence). The company requested advice regarding outcomes, comparators, trial design, population, real-world evidence and economic modelling.

HTA agencies from across nine countries were participants and a regulatory agency (EMA) was a participant in one meeting and an observer at three. The Sanofi team, who were surveyed regarding their SEED pilot participation, experienced a high level of satisfaction in relation to the collaboration with external partners.

Evaluating multi-stakeholder scientific advice

In the second part of the CIRS survey, participants were asked to evaluated three different programmes of multi-stakeholder advice:

- European Medicines Agency (EMA) parallel advice with HTA agencies;
- European Network for Health Technology Assessment EUnetHTA) pilot "Early Dialogues" and
- "Shaping European Early Dialogues (SEED) "pilots between its member HTA agencies and sponsors of health products currently in the development stage.

"The SEED and EMA/HTA programmes were evaluated as being approximately equal in terms of process and quality compared with the ratings for the EUnetHTA early dialogue.

When rated for its impact on outcome, the SEED programme was assessed as slightly superior to both of the EMA/HTA parallel advice programme and the EUnetHTA programme."

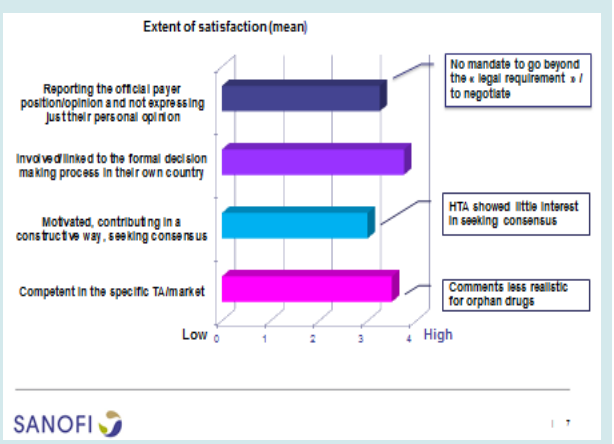
Neil McAuslane

Survey results also showed that

- 58% of survey participants observed divergence between regulatory and HTA advice especially in choice of the active comparator; acceptable endpoint; patient selection and trial duration and
- 83% observed divergence among HTA agency advice, especially in choice of the active comparator; acceptable endpoint; quality of life measurement and patient population.

Although some Forum participants maintained that multi-HTA agency advice is the most useful, survey results and the experience of several participating companies indicated that scientific advice meetings with active participation from regulatory and HTA agencies may prove worth the additional manpower and planning.

The Sanofi team experienced a high level of satisfaction in their interactions at the SEED meeting



" . . . approximately twice as much time and resources were dedicated for the meeting for the rare disease therapy, which was the meeting at which the EMA acted as a participant rather than an observer. However, this internal investment resulted in distinct benefits and outputs for Sanofi including better alignment on the product value proposition and the early identification of needs and requirements."

Anouchka Vidal

"Roche has focussed on alignment of HTA and regulatory advice. Although HTA or payer agencies may sometimes demonstrate a lack of flexibility, positive outcomes have been realised where alignment with regulators could be achieved."

Jens Grueger

Forum session 2: How can we measure the success of a scientific advice meeting? Which is the optimal pathway?

Overcoming limited agency resources

In some ways, requests for HTA scientific advice have become competitive, as agencies now find themselves inadequately resourced to handle the growing number of industry requests. Forum participants explained that it may take six months or more to get an appointment for scientific advice from HTA agencies, during which time changes to the development plan occur that may have an impact on the request for scientific advice.

Roundtable discussants recommended that industry invite three or four key countries for HTA advice, adding other countries on a rotational basis. It is likely that the jurisdictions of primary interest will have greater resources than smaller agencies, which may alleviate timing and capacity issues. Other recommendations were also suggested.

Recommendations

- Agencies should perform triage via teleconference or prepare prior written requests for individual points of clarification to improve review efficiency and timelines.
- Agencies should develop guidance and frequently-asked-questions documents to guide the focus on the key questions for a particular programme.

Measuring the success of advice

"Most of CIRS survey participants indicated that the success of scientific advice was measured by its impact on a product development plan such as

- *the adoption of the scientific advice in the development plan;*
- *an improvement in the development plan, agreement or confirmation of study design;*
- *or even by termination of the development plan.*

Other measures included

- *a qualitative assessment by meeting participants;*
- *the quality of interaction with HTA agencies;*
- *the potential to bridge divergence between regulatory and HTA requirements and*
- *the willingness to return for more HTA scientific advice meetings."*

Neil McAuslane

Recommendations

- To measure the effectiveness of scientific advice, companies should determine if this has resulted in a confirmation of internal decisions or a change in development programme.
- Companies should determine the extent to which HTA organisations have learned about the practical and ethical regulatory issues that companies face in evidence generation and if companies have gained a better understanding of the elements needed to support an efficient HTA process.

Effective pathways for HTA advice

Some of the elements for an effective pathway for HTA scientific advice listed by companies in the CIRS survey included clear agency criteria for initiating advice, identifying defined agency contacts, sharing timelines and processes, clarifying pre-meeting interactions, having sufficient time to develop briefing documents, the best ways to focus high-level discussions on phase III design and real-world evidence generation, having the flexibility to discuss product or portfolio issues and the incorporation of pricing discussions. Specified pathway outcomes included binding practical advice that accounts for costs and benefits and that identifies issues for alignment among HTA agencies or potential points of compromise.

They preferred a pathway that included the EMA and multiple, well-informed, well-resourced, consistent HTA agencies and flexible participation from multiple stakeholders through multiple meeting formats that conformed to specific needs.

Maximising the long-term value of HTA advice

Communicating with HTA agencies regarding the rationale for planned uptake of advice may add to the value of future advice sessions. In addition, companies should rely on the institutional memory regarding regulatory requirements and processes that has been conferred by decades of regulatory experience and similarly aim to take full advantage of HTA advice.

Recommendations

- Companies should provide feedback to HTA agencies on which elements of advice will be taken up and why.
- Companies should develop a database of collected learnings and accrued information from HTA scientific advice. Methods of disseminating this expertise and experience such as workshops should be implemented.

Summary of key points

COMPANY ASPECTS

Very few of the companies that participated in the CIRS survey had a strategy for seeking early HTA scientific advice for every new development programme; this strategy is usually developed on a case-by-case basis. Once it was determined that scientific advice would be solicited for a product, most companies either had or were developing a process that specified from whom, when and on what topics that advice would be sought.

Most surveyed companies indicated that they first seek HTA advice during phase II development. However, because product development teams should consider HTA requirements when building a product profile, late phase II may be too late to make any needed major changes to a development plan. The majority of companies in the CIRS survey seek HTA scientific advice at multiple time points in development and this advice can yield an ongoing benefit.

Many internal industry stakeholders are not convinced of the value of HTA scientific advice, and competing priorities within the organisations sometimes create a gap between receipt of the advice and its implementation in product development. Early understanding of business priorities for the company such as intended rollout timing is critical, as scientific advice strategy for products, such as from where the advice will be sought and whether it will be joint advice from multiple stakeholders, will flow from those priorities.

Project management, particularly timeline management, presents challenges to the receipt and implementation of early HTA scientific advice. A company's regulatory team should be considered a significant resource because their established project management systems are key to scheduling and monitoring the outcomes of regulatory scientific advice. Additionally regulatory colleagues are skilled at understanding how to interact at advice meetings based on previous experiences with regulators and have medical writing support to advise how to prepare briefing documents.

HTA AGENCY ASPECTS

Because of increased demand for HTA advice, delays in scheduling advice sessions have been reported. To alleviate resource constraints, HTA agencies should develop guidance and frequently-asked-questions documents to allow companies to bypass questions that may be common to all programmes and to focus on the key questions for a particular programme. Performing triage via teleconference or prior written submissions for individual points of clarification might also improve review timelines and allow a better focus for the face-to-face interaction

Some of the elements for an effective pathway for HTA scientific advice listed by companies included clear agency criteria for initiating advice and defined agency contacts, timelines and processes, pre-meeting interactions, sufficient time to develop briefing documents, focussed high-level discussions on phase III design and real-world evidence generation, flexibility to discuss product or portfolio issues and the incorporation of pricing discussions . A pathway that included a regulatory agency such as EMA and multiple, well-informed, well-resourced, consistent HTA agencies was preferred and flexible participation from multiple stakeholders through multiple meeting formats that conformed to specific needs.

Despite potentially complex logistics and intensive use of resources, a multi-HTA strategy was considered optimal because pre-meetings with HTA bodies ensure that although there may be disparities, there is an increased probability of alignment and a cohesive viewpoint. Industry should use a decision tree to decide which questions to be asked and stakeholders to engage in multi-HTA advice consultations. Companies should ensure that participants have decision-making ability.

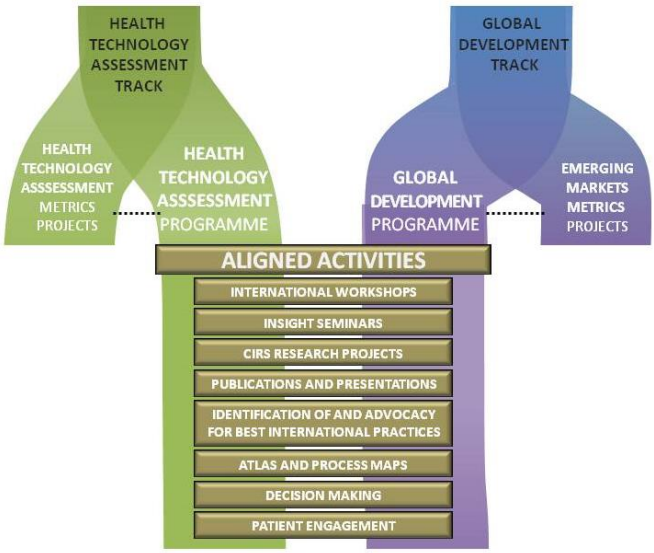
To measure the effectiveness of scientific advice consider its impact on a product development plan such as its adaptation, improvement, confirmation or termination. Other measures include a qualitative assessment by meeting participants, the quality of interaction with HTA agencies, the potential to bridge divergence between regulatory and HTA requirements, the willingness to return for more HTA scientific advice meetings and whether HTA organisations have learned about some of the practical and ethical regulatory issues that companies face in evidence generation and if companies have gained a better understanding of the elements needed to support an efficient HTA process.

Long-term optimisation: Companies should provide feedback to agencies on which advice will or will not be taken up and why; consider the compilation of repositories of accrued information on HTA-related scientific advice as well methods of disseminating internal expertise and experience such as workshops.

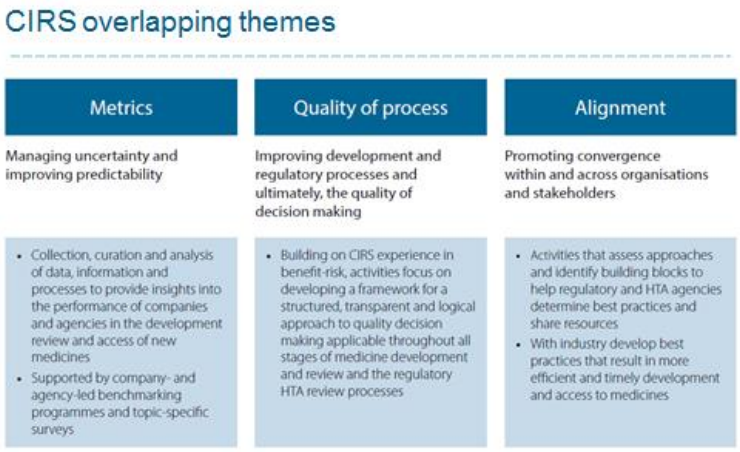
The Centre for Innovation in Regulatory Science

The Centre for Innovation in Regulatory Science
CIRS provides a neutral, independent, 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. CIRS achieves its mission of advancing regulatory and HTA policies and processes by means of the aligned activities of its Health Technology Assessment and Global Development programmes – activities that include international Workshops, Insight Seminars, research projects, publications and presentations and the identification of and advocacy for best international practices.

Through these activities, CIRS regularly interacts with international pharmaceutical companies, regulatory agencies and HTA and coverage bodies to address the overlapping themes of *metrics*, to manage uncertainty and improve predictability; *quality of process*, to improve the development of development, regulatory and health technology assessment processes and ultimately the quality of decision making and *alignment,* promoting convergence within and across organisations and stakeholders.



CIRS has organised its activities into the Global Development and Health Technology Assessment programmes.



Through its research, Workshops and other activities, CIRS focuses on the themes of metrics, quality of process and alignment.

CIRS HTA programme activities

- **International Workshops** facilitate networking, constructive discussion, recommendations and actions.
- **Industry and agency-supplied and publicly available data** are collated by CIRS into informative HTA performance measures, which enable contextualisation of review procedures across various jurisdictions.
- **The CIRS Regulatory & Reimbursement Atlas** systematically maps regulatory review to reimbursement in more than 70 countries/jurisdictions.
- **Surveys and other research** focus on specific areas of interest within pharmaceutical regulation, HTA and government affairs.
- **Insight seminars** for member companies and meetings with HTA agencies centre on HTA programme research outcomes.
- **Technical fora** concentrate on timely topics of special interest to industry