Summary from FINOSE Strategic HTA and Industry Meeting

FINOSE

March 27, 2018

Statens legemiddelverk
Norwegian Medicines Agency

fimea

TLV

BACKGROUND TO THE MEETING

On March 27, 2018 the three Nordic HTA agencies – Sweden's Dental and Pharmaceutical Benefits Agency, the Norwegian Medicines Agency and the Finnish Medicines Agency gathered representatives from the European HTA community – from European Commission level to individual agencies country by country – and the global pharmaceutical industry to discuss two current topics:

- The move towards cross-country collaboration by European HTA agencies
- How Real-World Evidence can make a difference in HTA decision making

The group gathered at Stallmästaregården in Stockholm for a day of networking and discussion. This note is a summary of the discussions that were held among this group.



THE MOVE TOWARDS CROSS-COUNTRY COLLABORATION BY EUROPEAN HTA AGENCIES

Already in 2004, the European Commission and Council of Ministers declared joint health technology assessment (HTA) to be a priority area for the European Union. The first joint activities were established under the leadership of a EUnetHTA project in 2006 and following a series of joint actions between member countries since then, a permanent cooperation of EUnetHTA is to be established after 2020. In this current period, ranging from 2016-20, EUnetHTA is focusing on the following priorities:

- Coordination across member countries' HTA bodies
- Dissemination of EUnetHTA deliverables and progress
- Evaluation of implementation and the uptake of EUnetHTA products
- Production of joint health technology assessments
- Generation of evidence for health technologies (e.g., early evidence generation, post-launch evidence generation and registries)

- Establishment of quality management tools for the HTA collaboration on EU level
- Support to the practical implementation of the HTA cooperation

In parallel to EUnetHTA – while still adhering to the overarching principles of EUnetHTA, at least four different geographic HTA "constellations" or collaborations have emerged. Each with a different structure and set of guiding principles. The formation of these groups implies that today only a small number of European Union countries intend to operate outside such a collaboration.

An overview of the largest existing regional collaborations in Europe today

BeNeLuxAIr (Belgium, Netherlands, Luxembourg, Austria and Ireland)

In 2016, the Belgian, Dutch, Luxembourg and Austrian governments declared their intention to collaborate on pharmaceutical policy, more precisely on horizon scanning (HS), health technology assessment (HTA), information sharing and policy exchange, and pricing and reimbursement. It is the goal of the collaboration to avoid duplication of efforts by dividing tasks and sharing data. Later, Ireland joined the constellation.

La Valetta Group (Italy, Spain, Greece, Portugal, Slovenia, Cyprus, Malta, Croatia and France as an observer)

La Valetta was established in May 2017 with the intention to, among others, guarantee patients access to new, innovative treatments and ensure sustainability of the participating national health systems. Apart from exchanging best-practices across the countries, the collaboration is engaged in the following different activities:

- Gathering and sharing information (e.g., policies and reimbursement decisions)
- Horizon scanning of innovative medicines and treatments
- Joint clinical assessments and economic evaluation
- Exploring joint price negotiations

FINOSE (Finland, Norway, Sweden)

FINOSE was launched on the day of the conference, March 27th, 2018. The overall intention of the collaboration is to ensure earlier access to drugs through cooperation on assessment of relative efficacy and relevant parts of the health economic framework. A joint team across the three countries will be assigned to share work for accepted applications and reduce the regulatory burden on both the agencies and the applying pharmaceutical companies (i.e., simultaneous submission to the three agencies). The access and reimbursement decision is still subject to the individual agencies' national regulations country-by-country.

FINOSE are now receiving applications for joint assessment and the pilot will run until 2020.

Visegrad (Czech, Hungary, Poland, Slovakia, Croatia, Lithuania)

The mandate of Visegrad is still relatively unclear and no participants visited the conference. However, the collaboration has indicated an intent for joint price negotiation.

What does the emergence of regional collaborations mean for HTA and industry?

The emergence of regional collaborations across Europe will have an impact both on HTA bodies' internal processes and outputs, as well as industry submissions and marketed products. Some of the likely effects that can be expected are:

- Reduced workload and time to market: If clinical and cost effectiveness assessments and to some extent pricing can be performed across several countries at the same time, both workload and time can be spared. This is especially true for HTA bodies, who can split the internal workload across agencies. However, also pharmaceutical companies can expect reduced workload if the total number of submissions are reduced.
- Less divergence in HTA methodologies and evidence requirements: Joint processes can create an alignment on submission requirements, methodologies and bars for evidence across cooperating countries. In the short term, joint processes promise to reduce complexity in industry submissions in European markets, as the spectrum of different approaches used by HTA bodies is significantly reduced. It can also mean less variation in assessment outcomes, which could have both positive and negative effects on launches of new pharmaceuticals. In the medium to long term, this development could even help stimulate the effective development and use of Real-World Evidence. With a smaller group of principals setting the direction for approved methodologies and bars for evidence, more clarity will be shed upon what industry and regulators need to achieve.
- New possibilities for innovative pricing models: Managed entry agreements are often used to overcome difficulties related to lack of data and uncertainty in the market entry. These agreements can connect pricing to the collection of data in real world usage. Several, but not all, of the already formed geographic collaborations have the explicit intent to increase collaboration on pricing. Increased collaboration across borders will likely create new opportunities for innovative pricing models because of a larger patient population for data collection, especially in the case of rare diseases. This kind of harmonized data collection from larger population could also help the manufacturer to fill the regulatory needs for additional data. Consequently, increased collaboration may lead to more acceptable pricing models of new pharmaceuticals and thus, better access to patients.

Effective collaboration across geographies is still a relatively unproven concept, and while collaboration is likely to increase in the next few years, challenges such as variations in legislations across the cooperating countries still prevail. However, in the long term, this can be the first step towards a single EU submission template, which carries the potential to simplify alignment with EMA evidence requirements in, for example, adaptive pathways.

HOW REAL-WORLD EVIDENCE CAN MAKE A DIFFERENCE IN HTA DECISION MAKING

Background – why do we need Real World Evidence?

Across health systems in the developed world, the cost of providing healthcare to citizens is growing faster than GDP. The imperative for ensuring 'value for money' has never been stronger and can be seen in many parts of the healthcare systems. Payors are increasingly implementing systems for measuring quality of care and reimbursing healthcare providers on quality outcomes. For pharmaceuticals, national spending has increasingly been pressured through cost containment measures such as rebates and caps on expenditure over the last 10 years.

Up until today randomized clinical trials (RCT) remain the main option to evaluate the efficacy and safety of new pharmaceuticals, as well as providing a basis for setting pharmaceutical pricing. While the methodology for running RCTs is well-established and has clear strengths, such as being unbiased and consistent, it also poses limitations. Trial patients do not represent the real population, and it is impossible to say if the patients were representative. In addition, trials are conducted for a limited period and do not show the long-term effects of drug treatment. The transparency into whether the payor has achieved 'value for money' for patients prescribed a specific drug is therefore low.

Across healthcare systems, payors and other regulatory bodies are exploring ways to contract pharmaceutical pricing based on actual health outcomes. The development of evidence from usage of drugs in the real world – Real World Evidence (RWE) – is a potential method to supplement what we learn from RCTs. This is true for pharmaceuticals overall, but especially important for innovative treatments when the RCT data provides limited insight, e.g., in the cases of:

- *Rare diseases* or *personalized medicine*, where the patient population is so small that findings are difficult to extrapolate to the population as a whole
- *Combination therapies for oncology,* where a multitude of combinations are possible and no single combination has been proved optimal
- *Drugs introduced using adaptive pathways*, where the Phase II approval data might be too limited for traditional health technology and cost effectiveness assessments

Data on pharmaceutical use in clinical practice, combined with demographic, socioeconomic and other third-party data, promise new insights on the effect of drug usage for the population overall and in different sub-populations. The data will support evidence of drug effectiveness, but also help make health technology and cost effectiveness more targeted to the actual value that a drug provides for different indications and sub-populations. On that basis, a pathway for outcome based contracts ("pay for performance") between regulators and industry would seem within reach.

Where are we today on the use and development of Real World Evidence?

So far there are not large numbers of outcomes based contracts existing between payors and the pharmaceutical industry. While selected examples exist – e.g., in the US where individual payors have begun contracting on "pay-back" for non- responders or in Italy where pharmaceutical companies

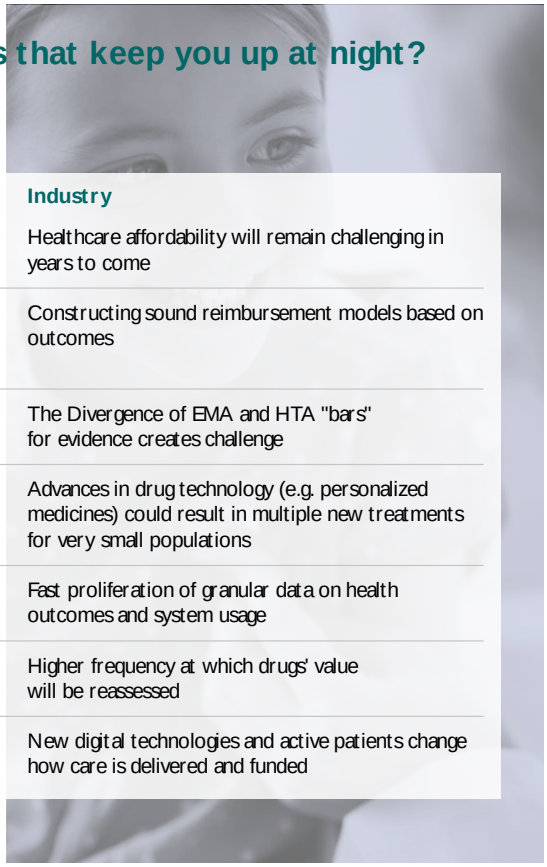
are required to include new drugs on national registries which then become the base data for managed entry agreements – no-one system has consistently solved the challenges.

In the FINOSE strategic HTA and industry meeting in Stockholm on March 27th, 2018, the three organizing organizations – the Swedish Dental and Pharmaceutical Benefits Agency , the Norwegian Medicines Agency and the Finnish Medicines Agency – intended to understand what might get in the way of outcome based contracting and what both sides of the table, "HTA and Government" and "Industry", could do to solve issues.

As a starting point, the attendees were asked to rank a list of pre-defined challenges from most important to least important. Responses were similar across the two groups, apart from one category, as can be seen in Graph 1.

- Both groups rated two among the top challenges: '*Healthcare affordability will remain challenging in years to come'* and '*Constructing sound reimbursement models based on outcomes'*
- Similarly, both groups rated challenges '*Higher frequency at which drugs' value will be reassessed'* and '*New digital technologies and active patients change how care is delivered and funded'* as least important
- A difference in opinion was noted for '*The Divergence of EMA and HTA "bars" for evidence creates challenge',* where industry see this as a more significant challenge than HTA and Government bodies

Graph 1: Which are the top challenges that keep you up at night?
(Most important at top)



	HTA and Government	Industry
1	Healthcare affordability will remain challenging in years to come	Healthcare affordability will remain challenging in years to come
2	Advances in drug technology (e.g. personalized medicines) could result in multiple new treatments for very small populations	Constructing sound reimbursement models based on outcomes
3	Constructing sound reimbursement models based on outcomes	The Divergence of EMA and HTA "bars" for evidence creates challenge
4	Fast proliferation of granular data on health outcomes and system usage	Advances in drug technology (e.g. personalized medicines) could result in multiple new treatments for very small populations
5	Higher frequency at which drugs' value will be reassessed	Fast proliferation of granular data on health outcomes and system usage
6	The Divergence of EMA and HTA "bars" for evidence creates challenge	Higher frequency at which drugs' value will be reassessed
7	New digital technologies and active patients change how care is delivered and funded	New digital technologies and active patients change how care is delivered and funded

The group was also asked what challenges might be missing from the list. Answers can be summarized along three different themes:

- *Lack of trust and constructive dialogue:* Both groups indicated that the mutual lack of trust and constructive dialogue between regulatory bodies and the private industry creates a divide that gets in the way of open and creative collaboration.
- *Misaligned incentives:* Both groups also indicated that the two groups' incentives might not focus on the same endpoint. Comments such as "National authorities are afraid to lose control of reimbursement decisions" or "Industry addicted to high margins" illustrate that a common ground for agreement is not place.
- *Applying RWE in practice:* Across groups many commented on the different challenges of really making use of RWE in practice. This ranged from getting payors to engage in collection of outcomes data to release relevant datasets for these purposes, to updating and adapting HTA methodologies for new types of evidence, data quality and processes.

Throughout the discussions, selected meeting participants – both HTA and industry – shared experiences and examples of applying RWE in practice. Based on their experiences, the two groups were asked to rank which challenges were most important to solve in co-operation between HTA agencies and industry, as can be seen in Graph 2.

Graph 2: Which are the top challenges where cooperation between industry and HTA is crucial to address the challenge?
(Most important at top)

	HTA and Government	Industry
1	Constructing sound reimbursement models based on outcomes	Constructing sound reimbursement models based on outcomes
2	Healthcare affordability will remain challenging in years to come	The Divergence of EMA and HTA "bars" for evidence creates challenge
3	Advances in drug technology (e.g. personalized medicines) could result in multiple new treatments for very small populations	Healthcare affordability will remain challenging in years to come
4	The Divergence of EMA and HTA "bars" for evidence creates challenge	Fast proliferation of granular data on health outcomes and system usage
5	Fast proliferation of granular data on health outcomes and system usage	Higher frequency at which drugs' value will be reassessed
6	Higher frequency at which drugs' value will be reassessed	Advances in drug technology (e.g. personalized medicines) could result in multiple new treatments for very small populations
7	New digital technologies and active patients change how care is delivered and funded	New digital technologies and active patients change how care is delivered and funded

The two top-ranked challenges from the first poll also ranked in the Top-3 on both groups' list for this poll; both HTA agencies and industry wants to see increased collaboration to counter challenges '*Healthcare affordability will remain challenging in years to come'* and *'Constructing sound reimbursement models based on outcomes'*. The third Top-3 challenge on the HTA and industry list

respectively had a closer link to the two groups' respective day-to-day challenges. Industry wanted to see collaboration around creating a '*joint bar for evidence between HTA and industry'*, while HTA agencies wanted collaboration around *'how advances in drug technology could result in multiple treatments for very small populations'*.

In summary, to move the needle on continuous application of RWE in HTA decision making the following is needed:

- HTA and industry need to meet and establish relationships on a strategic level on a regular basis. These relationships need to be characterized by transparency and mutual trust
- The underlying rules for pharmaceutical pricing and reimbursements needs to be redefined in the light of using RWE. Stakeholders– from regulator to manufacturers – need to discuss e.g.,
  - Which are appropriate methodologies for developing RWE?
  - What should the guidance and requirements be when using RWE (e.g., minimum standard datasets), and how should it be used in relation to RCT data?
  - How pricing and reimbursement decisions set using RWE – and will this be reviewed over time?
- Collaborations across industry and payor/regulators needs to be explorative and allow a pragmatic 'try-and-fail' approach using the data and capabilities that are available. At the same time, regulators/payors need to be quick to transfer new knowledge into clear standards to create predictability and clarity for the industry.

* * *

The three hosting agencies would like to thank all the participants for their valuable contributions during the conference. The discussions and reflections will be highly valuable to all our three agencies as we continue to develop efficient systems to provide citizens and patients with the pharmaceutical products they need. There has already been follow up meetings in the three countries and we hope to see the FINOSE cooperation receiving its' first application soon.