Impact of HTA (Health Technology Assessment) requirements on SMEs (Small and Medium sized Enterprises) in Europe

Prepared by SFL Regulatory Affairs & Scientific Communication Ltd
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EuropaBio mission is to promote innovative and dynamic biotechnology-based industry in Europe. EuropaBio (the European Association for Bioindustries) has 66 corporate and 7 associate members operating worldwide, 4 Bioregions and 22 national biotechnology associations representing some 1800 small and medium sized enterprises. EuropaBio conducted the literature search and co-authored the report.

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1 Executive Summary

To evaluate new treatments in a more systematic way, governments increasingly turn to health technology assessment (HTA). Information from HTA, such as clinical effectiveness and cost effectiveness, is used by authorities to take decisions on pricing and reimbursement. Anecdotal evidence indicated that SMEs in particular were finding it challenging to adjust to the increasing use of HTA as they strove to bring their products to the market and gain reimbursement.

In order to better understand how the use of HTA impacts SMEs’ R&D efforts and market access opportunities, a survey was conducted by SFL Regulatory Affairs & Scientific Communication Ltd and EuropaBio. The survey looked at how European SMEs consider HTA throughout the different stages of drug development, from the pre-clinical phase through marketing authorisation and to the post-marketing stage. It also aimed to identify potential hurdles that SMEs face when dealing with HTA.

The results indicate that the general knowledge of HTA requirements and processes is poor among biotech SMEs. Very few SMEs have staff with HTA expertise, with most relying on consultants and licensing partners. It is noteworthy that high competitiveness in the market place is associated with the acquisition of HTA expertise by SMEs.

HTA is almost not considered in SMEs’ clinical trial design or other key decisions during the development stage, probably due to lack of in-house expertise or other resource issues.

Moreover, the survey indicates an apparent lack of communication between SMEs and HTA agencies.

The lack of understanding of HTA processes and uses is perceived by SMEs as the most challenging aspect of HTA, next to finding a comparator accepted as standard of care. Some SMEs also found the decision criteria of HTA agencies unclear.

Three SMEs had to end their development/marketing efforts due to actual or foreseen failure to provide sufficient evidence for HTA. This is a worrying tendency since SMEs are key contributors to new and improved medical treatments, and a key research partner to large, established biotech- and pharmaceutical companies. If these biotech SMEs are unable to thrive, their products may never reach patients who may then miss out on crucial life-improving treatments.

Support in the area of HTA is therefore vital to maximize biotech SMEs’ chances to successfully reach the market and gain funding for important treatments for patients.
2 Glossary

Pre-clinical – the pre-clinical stage is the stage of product development when the substance has not yet been tested on humans, only in a laboratory setting.

Clinical phase – Refers to the stage of the clinical trial process.

Phase 1 – The first phase of a clinical trial, which usually involves a low number of participants and has the purpose to determine the best delivery method, best dosage and most importantly if the treatment is safe for humans.

Phase 2 – The second phase of a clinical trial which involves more participants than phase 1 and is carried out to determine if the treatment is effective on patients. It also provides additional safety data.

Phase 3 – The third phase of a clinical trial with the purpose to determine if the new treatment works better than the established current treatment for the same disease/condition.

Marketing authorisation application (MAA) – An application for authorisation to place medicinal products on the market.

Market access – An opportunity for a company to enter a specific market to commercialise its products or services.

Health Technology Assessment (HTA) – HTA is a research-based assessment of the medical, economic, social and ethical implications of the incremental value, diffusion and use of a medical technology in health care.

HTA authority – A national body tasked with carrying out HTAs for prospective new medical technologies (e.g. the UK’s National Institute for Clinical Excellence-NICE).

Small and Medium Size Enterprise (SME) – In the EU, the European Medicines Agency defines an SME as a company with no more than 250 employees, annual turnover not in excess of €50 million and a balance sheet not exceeding €43 million.

Pivotal clinical trial – A trial which provides the significant evidence which enables the “cost-benefit” analysis of a HTA authority.

European Medicines Agency (EMA) – The European Medicines Agency is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

Research and Development (R&D) – In the context of commerce, “research and development” normally refers to future-oriented, longer-term activities in science or technology, using similar techniques to scientific research without predetermined outcomes and with broad forecasts of commercial yield.

Orphan disease – A rare disease that affects a small percentage of the population.

Indication – the purpose for which a certain medical technology such as a test, medication, procedure, or surgery, is used and approved.

Pricing and Reimbursement (P&R) – Pricing refers to the direct or indirect setting of pharmaceutical prices by Member States. Reimbursement refers to the process of a state paying back (reimbursing) a patient the cost of a medicine approved for reimbursement. Systems differ throughout Member States with some reimbursing to a point, others fully.
3 Introduction

About HTA in Europe

Health technology refers to any method that is used to promote health, prevent, diagnose and treat diseases or improve rehabilitation and long-term care. Technologies include drugs, devices, diagnostic agents, equipment, and medical and surgical procedures.

Health Technology Assessment (HTA) is “the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods”.

HTAs provide high-quality information to decision makers about the clinical effectiveness, cost-effectiveness, and broader impact of drugs, medical technologies, and health systems. Many EU Member States have established HTA systems to systematically determine the relative “value for money” provided by new technologies – including biotech medicines – to, ultimately, support decision-makers in their coverage, pricing and reimbursement decisions. These HTA systems give providers and patients information with which to make treatment choices. The systems also encourage the efficient and effective use of health technologies and support innovation by identifying and rewarding high-value products.

It is important for companies and especially SMEs to have a good grasp of the use of HTA by government bodies in countries of relevance for them, as often the use of HTA is closely or directly linked to a reimbursement decision, which in turn has a direct impact on market access. This issue is even more acute for SMEs than it is for larger companies.

However there is no European consensus on how to value and reward healthcare innovation. HTA mechanisms to evaluate clinical and/or cost-effectiveness differ between EU Member States. In some healthcare systems, cost-effectiveness or cost-utility models with a limited systematic review of clinical data are presented as HTA and are considered to have the statute of a holistic evaluation of technologies when they are not. Such HTA evaluations can have the impact of punishing research-intensive biotech SMEs and also threatening patient access by possibly serving as a tool of cost containment/rationing policies in healthcare, which may not prioritise the interests of patients.

There are stark differences between the situation in some of the old Member States and the Member States which joined the European Union in 2004. A detailed analysis of the HTA situation in those new Member States concluded that socio-economic pressures in these countries have caused the onus to be placed on a need for value for money and therefore on HTA, which is why there have been significant developments in this field. However, those Member States face economic and academic (e.g. lack of training opportunities) challenges in catching up to older Member States in the HTA field. Several EU Members States are still lacking a dedicated HTA body, contrasting to established European bodies such as the UK’s NICE.

Situation for life science SMEs in Europe

A company is considered a small and medium-size enterprise (SME) when its number of employees is less than 250 employees. In the European Union, it is estimated that there are about 23 million SMEs representing 99% of all enterprises and accounting for two-thirds of all

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1 Definition from INAHTA (International Network of Agencies for Health Technology Assessment). Available at: http://www.inahta.org/HTA/Glossary/#_G
2 Such as The National Institute for Health and Clinical Excellence (NICE) in the UK, the Haute Autorité de Santé (HAS) in France or Institute for Quality and Efficiency in Health Care (IQWiG) in Germany
3 Cyprus, Czech Republic, Estonia, Hungary, Malta Latvia, Lithuania, Poland, Slovakia, and Slovenia joined the European Union in 2004
4 Sorenson, Kanavos & Karamalis “HTA in Central and Eastern Europe: Current Status, Challenges and Opportunities”
private-sector jobs. Globally, SMEs account for between 40 and 50% of GDP. In 2003, the European Commission adopted recommendations regarding the definition of an SME including criteria based on headcount and turnover. The table below summarises the recommended categorisation.

<table>
<thead>
<tr>
<th>Enterprise category</th>
<th>Headcount</th>
<th>Turnover</th>
<th>Or Balance sheet total</th>
</tr>
</thead>
<tbody>
<tr>
<td>medium-sized</td>
<td>&lt; 250</td>
<td>≤ € 50 million</td>
<td>≤ € 43 million</td>
</tr>
<tr>
<td>Small</td>
<td>&lt; 50</td>
<td>≤ € 10 million</td>
<td>≤ € 10 million</td>
</tr>
<tr>
<td>Micro</td>
<td>&lt; 10</td>
<td>≤ € 2 million</td>
<td>≤ € 2 million</td>
</tr>
</tbody>
</table>

This categorisation is used by the European Medicines Agency (EMA) when granting a company SME status.

Most European biotech companies are micro or small, research-intensive firms and thus they fall squarely into the SME category. They are active in all sectors of life-sciences from healthcare to industrial and agricultural applications, often working with larger companies to develop new therapeutic solutions. In fact, larger pharmaceutical companies are increasingly relying on external R&D, mostly performed by emerging SMEs.

SMEs face a number of specific challenges associated with both their abilities to develop as well as getting their products approved and commercialised. R&D in biotech is characterized by high-costs, high risks and a long term approach. As a result, many biotech companies remain non-profit for quite some time and this in turn means that they are often perceived as being too high-risk for external investment or that they simply cannot fulfil the criteria to sign financing contracts. In addition, most biotech SMEs are funded by external capital, rather than by their own generated income, which means that when external sources of capital dry up, the day-to-day funding for biotech companies also evaporates.

On the approval and commercialisation side, healthcare biotech products in particular have to undergo long and expensive development and approval procedures. Funding for these stages has often proved insufficient in the past. This situation has been further aggravated due to the increased global economic uncertainty in the past few years. EMA has put in place an SME Office which provides support and incentives to SMEs to navigate through the regulatory approval pathway. Despite these efforts to help SMEs, it might not be enough to enable them to commercialize their products.

Anecdotal evidence shows that after marketing authorisation, when SMEs aim to introduce a new product on the market, they face particular challenges to overcome market access hurdles such as the increasing assessments of medicinal products at national or regional level (i.e. the use of HTA) which inform pricing and reimbursement decisions.

Since these suspected difficulties for SMEs to deal with HTA requirements are only based on anecdotal evidence, there is a need to get a broader picture of whether and how SMEs consider HTA requirements in the development and potential marketing of their products.

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5 Eurostat and European Observatory of SMEs
6 Commission Recommendation (2003/361/EC) concerning the definition of micro, small and medium-sized enterprises
4 Methodology

Aims and objectives
The aims of the report were to better understand how the use of HTAs impact SMEs’ R&D efforts and market access opportunities for new products developed by these companies.

The objectives were to:
- Better understand if, how and when SMEs take HTA requirements into consideration when:
  - Developing a product;
  - Applying for marketing authorisation; and
  - Entering the market.
- Identify potential hurdles SMEs face when dealing with HTA requirements

The report comprises findings for SMEs based in the EU and Switzerland, active in the life science sector.

Data collection

Survey
Since very limited information about the impact of HTA on SMEs was available, it was decided to collect the necessary data through a survey to be completed by SMEs. The survey consisted of 27 questions with multi-choice answers. It was distributed in October 2010 in the English language to SMEs via 22 national biotechnology industry associations who were members of EuropaBio, as well as through extensive direct contact on the part of the EuropaBio secretariat with SMEs registered at the EMA SME office.

In addition, companies in the network of EuropaBio and SFL were pro-actively approached. Certain companies who exceeded the 250 employee SME limit only slightly, but who were identified as active in this field, were also approached in order to increase the number of participating companies.

SMEs could either complete the survey on-line or via e-mail.

Literature search
A literature search was conducted to identify relevant academic or press articles on the general role and requirements of HTA and on its impact on SMEs’ R&D efforts. Very few articles were found as it seems that the field has not been studied yet.

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7 This report only contains highlights of the results of the survey. The interested reader can request the full survey and the data by contacting EuropaBio (www.europabio.org).
5 Results

19 companies responded to the survey.

Knowledge level in SMEs on HTA and their external environment

Familiarity with HTA concept and uses

Only 2 SMEs who completed the survey claim to be "very familiar" with HTA. The other responders were evenly distributed between those who claim to be familiar with HTA, somewhat familiar HTA but not clear on its concept and uses, and those who have never heard of HTA (5 each).

Among the 7 SMEs who are "familiar" or "very familiar" with HTA, no common characteristics could be identified apart from being active in orphan indications (6 companies). However, it is worth noticing that orphan indications are by far the most common indication amongst the SMEs who took part in the survey (13). Therefore it is not possible to draw the conclusion that companies active in this indication are more likely than others to be familiar with HTA.

Naturally, the 5 companies that have never heard of HTA or are unclear about the concept also have no access to HTA expertise. None of the companies without HTA knowledge have a product authorized yet.

Question 6: How familiar are you with the concept and uses of HTA?

<table>
<thead>
<tr>
<th>Number of SMEs</th>
<th>Very familiar</th>
<th>Familiar</th>
<th>Familiar but unclear about concept/use</th>
<th>Never heard of</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Source of HTA expertise

Only 2 companies have in-house HTA expertise (1 feeling “familiar”, 1 “very familiar” with HTA) while 8 have access to HTA expertise through external sources. As many as 5 companies don’t have access to HTA expertise at all.

In order to provide a benchmark against which to assess the level of HTA expertise, the survey also included a question regarding which other, more “traditional” expertise areas, SMEs have access to, such as marketing and reimbursement expertise. The responses revealed that 3 companies have in-house marketing and reimbursement expertise (all which feel “familiar” or “very familiar” also with HTA) while the majority (11) of companies rely (either completely or
combined with internal resources) on external sources such as licensing partners and consultants. 2 companies have no access to marketing and reimbursement expertise.

Thus, the way SMEs acquire HTA expertise does not really vary from how they acquire other expertise, and it is only slightly more common to have access to marketing and reimbursement expertise than to specific HTA expertise.

**Question 13: Where does your HTA expertise come from?**

<table>
<thead>
<tr>
<th>Number of SMEs (n)</th>
<th>1: In-house</th>
<th>2: Licensing partner</th>
<th>3: Consultants</th>
<th>4: Mix of internal and external sources</th>
<th>5: Don't have HTA expertise</th>
<th>6: No response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

To save the fixed costs of establishing and maintaining expertise is considered as the main reason for using external consultants (9 companies either for marketing and reimbursement expertise or for HTA expertise). Difficulties in competing with bigger companies for competent staff were also mentioned as a reason for hiring consultants (2 companies).

The profiles of the only 2 companies who claim to have *in-house* HTA expertise did not show any clear similarities: they are respectively located in France and Switzerland, with 5-8 employees each and both companies were established after 2005. They are active in different indications and the competitiveness of their market places are not similar. Both companies have managed to get their products at least partly reimbursed. Interestingly, one of the companies was the only company among all respondents who reported that its licensing partner had actively asked if and how the SME had considered HTA requirements.

Amongst the 8 companies that rely either fully on external sources or on a mix of internal and external sources for access to HTA expertise, 4 already have products authorized and 3 have products in phase III. 3 have their products reimbursed, either partly or fully, and 1 company's product is pending reimbursement.

4 of them have out-licensed their products for further clinical development and/or for bringing the product to market and selling the product. None of them were asked by partners whether HTA was considered in development of the products.

**Investors and market environment**

For the purpose of the survey, market environment was defined as the competitive environment an SME operate in. This included the dynamism of the investment market and the level of competitiveness between SMEs.
Out of the 19 surveyed companies, investors had asked in only 2 cases whether the company had considered HTA requirements, and only 1 company stated that the consideration of HTA requirements had most likely been a deciding factor for the investment. Hence, the consideration of HTA requirements does not seem to be a result of outside pressure from a company’s investor.

Out of the 10 companies who stated that they have access to HTA expertise, as many as 4 are active in a very competitive market environment (more than 3 competitors) and 2 are active in a competitive environment (more than 2-3 competitors). This may indicate a link between high competitiveness of a market and a likelihood that SMEs active in that market have noted a need for and acquired HTA expertise.

Out of the 19 surveyed companies, 7 have managed to out-license their products; 4 of these have access to HTA expertise. 8 out of 19 companies have not out-licensed their products; only 2 of which have access to HTA expertise. In other words: it is twice as common to have access to HTA expertise for companies that have successfully out-licensed their product than for those who have not. Unfortunately, it was not possible to conclude from the survey responses whether the access to HTA expertise in these cases was triggered by the licensing partner actively asking for it. As many as 12 SMEs did not respond to the question or did not know if the licensing partner had asked the question.

**Question 21: Did your investor(s) ask if and how you have considered HTA requirements? If so, was it a deciding factor for the investment decision?**

<table>
<thead>
<tr>
<th>Number of SMEs (n)</th>
<th>Number of SMEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
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<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

1: No  2: Yes, but HTA was not a deciding factor for partnership  3: Yes, and HTA was most likely a decision criterion for our partnership  4: Not known  5: No response
**Consideration of HTA requirements in the product life cycle**

The survey gives the respondent the choice between 11 phases in the life cycle when answering a question about when and how they generally consider HTA (question 7). However for the purpose of providing a more accessible overview, the results have been grouped according to the phases where HTA is most commonly considered: Pre-clinical, Clinical (Phase I-III), Regulatory Approval and Reimbursement and marketing.

**Pre-clinical**

Only 4 out of 19 companies responded that they consider HTA already in the pre-clinical phase. 3 of these have managed to get their products authorized, of which 2 involve HTA experts in the discussions and decisions at the pre-clinical stage. Unfortunately, none of the companies who consider HTA in the pre-clinical phase knew at what stage they tend to contact their HTA authority. Therefore it is not clear whether such contacts are made in the pre-clinical phase at all.

In terms of the profile of companies that consider HTA as early as in the pre-clinical stage, 3 of these SMEs were active in orphan indications, all but 1 company was founded after 2004 and all 4 companies had between 8-15 employees.

**Clinical**

Firstly, it shall be noted that an overwhelming majority of SMEs in the survey, 17 out of 19, are involved in designing the clinical trials for their products.

Despite this, only 3 SMEs said they consider HTA requirements when designing the trials. These 3 said HTA had influenced their trial design in the following way/s: choice of comparator (2), inclusion/exclusion criteria (2), trial length and size (1), inclusion of patient-reported outcomes (1) and the collection of resource data alongside the clinical trial (1). 1 of these SMEs had already started their HTA considerations in the pre-clinical phase.

Most SMEs (14) do not consider HTA requirements during the clinical trial design. The most common reason for not doing so was the lack of in-house expertise (6 companies). 2 SMEs specified that it is too costly to bring in HTA expertise. One company explained that "HTA rules vary too much depending on the countries so we prefer to rely on traditional clinical assessment". One company responded that the consideration of HTA in clinical trials design "is not applicable to our product", although the same company had responded that marketing/reimbursement or HTA experts do take part in the discussions as well as decisions regarding clinical trial design. One company considered it too early to factor-in HTA considerations since they focus first on proof of concept study designs.

Based on the above results, it may appear safe to conclude that there is a clear lack of consideration of HTA requirements in the clinical trial design phase. However, the responses to another question give a slightly different picture: SMEs were asked in a separate question in what phase their marketing, reimbursement and/or HTA experts get involved in discussions/decisions. 6 companies responded that they involve such experts during the clinical trial design. This is twice as many as the above companies who say they consider HTA in the design of trials. This may mean that HTA experts are indeed involved in the process, but that HTA requirements rarely influence the final design of the clinical trial.

The most common reason (5) for SMEs not to involve such experts in the clinical trial design is that they have not established such functions/experts internally.
Question 7: During which development- or life cycle phase of your products are HTA requirements generally considered / discussed in your company (multiple answers possible)

![Bar chart showing the number of SMEs (n) considering HTA requirements in different phases.]


Regulatory approval (MAA)

4 companies consider HTA during the phase of their Marketing Authorization Application (MAA) to the regulatory authorities. However, none of them consider HTA for the first time during the MAA: they all start to consider it in the clinical phase.

Marketing/reimbursement/HTA experts tend not to be involved at all during the actual regulatory approval phase, according to the survey responses. However, 3 companies responded that such experts are involved in discussions regarding clinical trials in phase 3. (Phase 3 trials provide crucial data to support an MAA application).

Reimbursement and marketing

2 companies consider/discuss HTA at the stage of applying for reimbursement for the product, for the first indication. Their HTA experts tend to get involved at this stage. The companies had not indicated any consideration on HTA in any of the earlier development stages. Both had products currently pending reimbursement decision but not yet a product reimbursed.

None of the SMEs in the survey consider HTA requirements during the phases of product launch, or during the market authorisation and/or reimbursement phase for an additional indication or when a competitor enters the market.

4 companies responded that they don't know during which life cycle phase HTA is considered.

Two companies did not choose any of the 11 phase categories, but gave individual answers to the survey question:
"To date (Oct-2010), HTA considerations are factored-in while engaging for the search for partners to develop our products or investors in order to better understand their expectations. HTA considerations are not formally part of the drug development."

"We are a bridge between discovery and the market. Towards the end of the development process, we licence out the drug. Our licensee deals with reimbursement."

**SME interaction with HTA authorities**

5 SMEs had interacted with their HTA authority. The most common time to interact was at the time of MAA submission for a product's first indication and during the reimbursement process for the first indication (2 companies respectively).

6 companies have not interacted with their HTA authority so far. The reason for this was no time/not a priority (5). 4 companies responded they were not sure whom to contact. Only 1 company was unsure what the value of interaction with the HTA authority would be.

9 SMEs responded they were not aware of any initiative of their HTA authority to raise awareness and increase understanding of HTA requirements among SMEs. 6 didn’t know. No company reported any awareness of such initiatives. One company commented:

"....would highlight that to its best knowledge, very little is done at national member states to support SMEs in their efforts to develop innovative products such as ATMPs. For instance, an incentive to eventually consider a fair pricing/HTA, would be to have SME incentives brought from EU level to national levels such as Scientific Advice AND CTA fees reduction (i.e.; in Germany an ATMP CTA file evaluated by PEI is up to € 19,000.00. This is valid for each and every trial a sponsor would submit, whereas for France, the Sci Adv and CTAs are free of charge). Finally, no wonder that R&D expenses may lead to increased costs for a Company which in turn will factor this in the Price & Reimbursement (P&R) negotiations."

One company responded that it had been rejected when it tried to discuss potential and points relevant for reimbursement with HTA authorities.
Question 23: If you have not had any interaction with your HTA authority so far, what was the reason?

<table>
<thead>
<tr>
<th>Number of SMEs (n)</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not sure whom to contact</td>
</tr>
<tr>
<td>2</td>
<td>Not sure what the value would be</td>
</tr>
<tr>
<td>3</td>
<td>No time/not a priority</td>
</tr>
<tr>
<td>4</td>
<td>Licensing partner is responsible for interaction with the HTA Authority</td>
</tr>
<tr>
<td>5</td>
<td>No response.</td>
</tr>
</tbody>
</table>

Key challenges for SMEs to comply with HTA requirements

The two most common challenges for SMEs to comply with HTA requirements are the lack of understanding of HTA processes and uses and finding a comparator accepted as standard of care by the HTA authorities (5 responses each). Another challenge is that the decision criteria in their HTA authority are not clear (3 companies). Difficulty to recruit patients was the least challenging of the options provided with 2 responses.

5 companies provided their own comments on what they see as the key challenges:

“Choice of target population and link to SPC indication, level of evidence criteria, trial length and size”

“Not required for our product”

“Identifying adequate endpoints ___ design issues for the various Health Authorities and HTA” OR “too early stage, priority is now to show efficacy of product”

“It would be of utmost importance to understand how European SME status can be factored in at EU-National HTA/Price& Reimbursement negotiations (i.e.; priority access to market, better prices, fees alleviations, financial aspects, etc.)”

A majority of 12 SMEs responded that they had never dropped development/marketing efforts due to actual or foreseen failure to provide sufficient evidence for HTA.
3 companies had to drop efforts due to the above reason. One of them explained it was due to lack of access to appropriate comparator data, the other that the appropriate comparator was not used and that the primary endpoint was ok for registration but not for HTA. One SME simply stated “no need to pursue an effort if a drug does not bring any economic value”.

**Question 24: What are the key challenges for your company regarding compliance with HTA requirements (multiple answers possible)?**

![Bar chart showing the number of SMEs (n) for each challenge.]

- **1**: Don’t understand HTA processes and uses
- **2**: Not clear what decision criteria are used by our national HTA Authority
- **3**: Difficult to recruit required number of patients
- **4**: Identification of a comparator accepted as standard of care by HTA authorities (or reimbursement bodies)
- **5**: Not known
- **6**: Other
- **7**: No response.
6 Conclusions

The objective of the report was to investigate if, when and how SMEs take HTA requirements into consideration during different stages in a product’s life cycle – development, marketing authorisation and marketing. It was also to identify specific hurdles that SMEs face when dealing with HTA requirement.

While the results show evidence of trends among SMEs, the low number of responders means that there needs to be a note of caution about using this data as a basis for wide ranging conclusions on the assumption that they apply to all European life science SMEs.

Development phase – is HTA considered and if so how?
6 out of the 19 SMEs (less than a third) in the survey consider HTA requirements during the development phase: the pre-clinical and clinical development of a product. The most common reason for not considering HTA is the lack of in-house expertise in HTA, followed by too high costs to bring in external expertise.

The few (3) companies who replied that their clinical trial design has indeed been impacted by HTA requirements, reported an impact on several aspects of the design, such as the choice of comparator, inclusion/exclusion criteria, trial length and size, inclusion of patient-reported outcomes and the collection of resource data alongside the clinical trial.

Marketing authorisation phase - is HTA considered and if so how?
4 out of 19 SMEs (ca one fifth) consider HTA requirements during the phase of marketing authorisation application. All SMEs who consider HTA in this phase had already started the discussions much earlier, in the clinical phase. It is no surprise that there is not much activity on HTA in this phase; free text comments by SMEs in the survey reveal that they see HTA as an aspect of reimbursement, which requires either early consideration in the clinical phase or is regarded as the responsibility of the licensing partner who will often take the role to bring the product to the market and find funding for it.

Marketing phase – is HTA considered and if so how?
The marketing phase includes the time from application for reimbursement until the launch of the product on the market. Only 2 out of 19 SMEs consider HTA during this phase. Both companies consider HTA requirements during the phase of applying for reimbursement for the product and for the first time - no consideration of HTA during the clinical development stages was reported by these companies.

Thus, only 8 out of 19 SMEs (less than half) in the survey consider HTA requirements in any of the key phases of product’s life cycle: development, authorisation and marketing.

How does the overall knowledge level on HTA look in SMEs?
SME’s self-assessment of their knowledge of HTA reveals that very few (2) are “very familiar” with HTA, and as many as 5 have never heard of the concept. This corresponds to the findings regarding the “actual” expertise SMEs have. Indeed very few (2) have HTA expertise in-house, 11 rely on external sources such as consultants or licensing partners for HTA expertise, and 5 (the same that are not familiar with HTA) do not have access to such expertise at all.

What hurdles do SMEs face when dealing with HTA requirements?
The lack of understanding of HTA processes and uses was indicated by SMEs themselves as the most challenging aspect of complying with HTA requirements, next to finding a comparator accepted as standard of care by the HTA authorities.

Very few SMEs have on hand staff who are knowledgeable about HTA. This means that they both lack the expertise but also perhaps the understanding of the need to acquire this expertise. Furthermore, attempts to hire staff with such knowledge are stifled by funding issues.

An additional hurdle for SMEs is the lack of strong communication with national HTA authorities, with companies relating that there is a failure to communicate mandatory requirements on the part of national authorities.
Dear Madame/Sir,

Thank you for taking the time to complete this survey which is performed by SFL Regulatory Affairs & Scientific Communication Ltd (SFL) on behalf of EuropaBio.

The objectives of the survey are to:

i) Evaluate how Health Technology Assessment (HTA)\(^8\) requirements are considered by Small & Medium-Sized Enterprises (SMEs) in the development, authorization and marketing of medicinal products

ii) Identify the major needs and concerns of SMEs associated with the implementation of HTA requirements in their development programs

iii) Enable EuropaBio to effectively communicate the position of SMEs on HTA to public bodies (EU institutions and National Authorities)

Please be assured that your answers will be treated as strictly confidential and will be anonymized before analysis. No company related information will be forwarded to any third parties. However, to allow for follow-up if questions arise during the process, please provide your contact details on the separate sheet.

Please send the completed survey no later than 13 October 2010, by e-mail or fax, to Emile McHarsky-Todoroff at e.mcharsky-todoroff@europabio.org

You can also fill this questionnaire directly on-line by visiting: http://www.kwiksurveys.com/online-survey.php?surveyID=HKELKH_c32ac33d

Thank you for your contribution.

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\(^8\) Health Technology Assessment (HTA) is a multi-disciplinary field of policy analysis that examines the medical, economic, social and ethical implications of the incremental value, diffusion and use of a medical technology in health care (as per INAHTA (International Network of Agencies for Health Technology Assessment), HTA Resources http://inahta.episerverhotell.net/HTA/)
YOUR CONTACT DETAILS

1. General information

Name of company:

Your name:

Your function:

E-mail:

Phone:
QUESTION 1-5: DETAILS ABOUT YOUR COMPANY

2. Information about your company

<table>
<thead>
<tr>
<th>Year of founding of company:</th>
<th>No. of employees:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country:</td>
<td>City:</td>
</tr>
</tbody>
</table>

3. Please indicate how many products you have in the different development stages.

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Authorized</th>
<th>Post-authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan diseases</td>
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<tr>
<td>Cardiovascular diseases</td>
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<td>Oncology and haematology</td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Oncology and haematology</td>
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<td>Neurologic disorders</td>
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<td>Paediatrics</td>
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<td>Endocrinology and metabolism</td>
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<td>Nutrition</td>
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<tr>
<td>Skin disorders</td>
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<tr>
<td>Gastrointestinal system disorders</td>
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<td>Oral health</td>
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<tr>
<td>Eyes, Ears, Nose and Throat Disorders</td>
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<tr>
<td>Musculoskeletal disorders</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

4. If you have products on the market, are they reimbursed / funded for their intended indication? If more than one answer applies, please indicate the situation for your key product.

- Yes, fully reimbursed
- Yes, partly reimbursed (for example only in some countries)
- Not reimbursed
- Pending reimbursement decision
- Don’t know

5. How would you describe your market place? If you are active in several markets, please indicate the situation for your key product.

- No competitor (first to market)
- 1 competitor
- 2-3 competitors
- >3 competitors
QUESTION 6-11: YOUR APPROACH TO HTA

6. How familiar are you with the concept and uses of HTA?
   - [ ] Very familiar
   - [ ] Familiar
   - [ ] Familiar but the concept and uses of HTA are unclear
   - [ ] Never heard of it before today

7. During which development- or life cycle phase of your products are HTA requirements generally considered / discussed in your company (multiple answers possible)?
   - [ ] Pre-clinical
   - [ ] Phase 1
   - [ ] Phase 2
   - [ ] Phase 3
   - [ ] Before or during submission of Marketing Authorization Application (MAA) for first indication(s)
   - [ ] During the reimbursement process by the HTA Authority for first indication(s)
   - [ ] When the product is launched for first indication(s)
   - [ ] Before or during submission of MAA for additional indication(s)
   - [ ] During the reimbursement process by the HTA Authority for additional indication(s)
   - [ ] When competitor product enters the market
   - [ ] We don’t consider HTA requirements
   - [ ] Don’t know
   - [ ] Other, please specify
     __________________________________________________________
     __________________________________________________________
     __________________________________________________________
8. Is your company involved in designing the clinical trials for your products?
   □ Yes
   □ No (if no, please proceed with question 12)

9. Have you ever considered/discussed including HTA requirements in the design of your clinical trials?
   □ Yes
   □ No (if no, please proceed with question 11)

10. If “yes” to question 9, where has the HTA requirements most influenced in your clinical trial design (select up to 3 choices)?
    □ Choice of comparator
    □ Trial length and size
    □ Inclusion/exclusion criteria
    □ Inclusion of Patient Reported Outcomes
    □ Collection of resource data alongside clinical trial
    □ Other, please specify
    ______________________________________________________________________
    ______________________________________________________________________
    ______________________________________________________________________

11. If “no” to question 9, is there a reason for not considering/discussing HTA requirements in the design of your clinical trials (multiple answers possible)?
    □ Not convinced about value for our business
    □ Lack of in-house expertise
    □ Too costly to bring in external expertise
    □ We think there is value in considering HTA; however, in real life, inclusion of HTA as end points comes at unacceptable cost
    □ We think there is value in considering HTA; however the risk of unacceptable delay in the development process and market entry is considered too high
    □ Considering HTA requirements is not a key priority for us since our products are first to market for their indications. Therefore, it is sufficient to show “traditional” values such as safety and efficacy for the time being.
    □ Other reason (please explain):
    ______________________________________________________________________
    ______________________________________________________________________
    ______________________________________________________________________
QUESTION 12-21: HTA EXPERTISE IN YOUR COMPANY

12. Where does your marketing and reimbursement expertise come from?
   - In-house
   - Licensing partner
   - Consultants
   - Mix of internal and external sources
   - We don’t have marketing and reimbursement expertise

13. Where does your HTA expertise come from?
   - In-house
   - Licensing partner
   - Consultants
   - Mix of internal and external sources
   - We don’t have HTA expertise

14. If consultants are used, what is the reason?
   - Difficulty to compete with big companies to recruit competent staff
   - Too costly to establish and maintain in-house expertise

15. As a general rule, do marketing/reimbursement/HTA experts take part in your company’s discussions and decisions on clinical trial design (multiple answers possible)?
   - Yes, they take part in discussions
   - Yes, they take part in decisions
   - No (please give rationale and proceed with question 17):
     - No respective functions/experts in our company
     - Other reason (please explain)
       __________________________________________________________
       __________________________________________________________
       __________________________________________________________
   - Don’t know
16. At what stage were marketing/reimbursement/HTA expert(s) involved in the discussions/decisions?

☐ Pre-clinical
☐ Phase 1
☐ Phase 2
☐ Phase 3
☐ Before or during submission of MAA for first indication(s)
☐ During the reimbursement process by the HTA Authority for first indication(s)
☐ When the product is launched for first indication(s)
☐ Post-authorization
☐ Before or during submission for additional indication(s)
☐ During the reimbursement process by the HTA Authority for additional indication(s)
☐ When competitor product enters the market
☐ Don’t know

17. Have development /marketing efforts ever been dropped due to actual or foreseen failure to provide sufficient evidence for HTA in your company?

☐ Yes (if so why?)
  ☐ Lack of access to appropriate comparator data
  ☐ We did not use the appropriate end points
  ☐ We were aware of the appropriate end points but it would have been too costly/too time-consuming to assess and evaluate those end points
  ☐ Other reason (please explain)
    ____________________________________________________________
    ____________________________________________________________
    ____________________________________________________________

☐ No

18. Have you licensed any of your molecules/products to partners?

☐ Yes
☐ No (if no, please proceed with question 21)
19. What was the reason for out-licensing? If the answers are different from product to product, please provide the answer based on the situation for your key product/molecule (multiple answers possible).

- For further pre-clinical development
- For clinical development
- For bringing the product to market incl. reimbursement
- For marketing and selling the product

20. Did your partner(s) ask if and how you have considered HTA requirements? If so, was it a deciding factor for partnership?

- The partner did not ask
- Yes, the question was asked but not a deciding factor for partnership
- Yes, the question was asked and most likely a decision criterion for our partnership
- Don't know

21. Did your investor(s) ask if and how you have considered HTA requirements? If so, was it a deciding factor for the investment decision?

- The investor/s did not ask
- Yes the question was asked but not deciding factor for investment
- Yes the question was asked and most likely a deciding factor for the investment
- Don't know
QUESTION 22-26: YOUR INTERACTION WITH HTA AUTHORITIES

22. When do you normally approach your HTA authority to discuss HTA requirements?
   If your approach differs from product to product, please indicate the most common approach or the approach you applied for your key product.
   - Pre-clinical phase
   - Phase 1
   - Phase 2
   - Phase 3
   - Before and during submission of MAA for the first indication(s)
   - During reimbursement process by the HTA Authority for the first indication(s)
   - When the product is launched for first indication(s)
   - Before or during submission for additional indication(s)
   - During reimbursement process by the HTA Authority for additional indication(s)
   - Never, we have not had any interaction so far with the HTA Authority
   - Don’t know

23. If you have not had any interaction with your HTA authority so far, what was the reason?
   - Not sure whom to contact
   - Not sure what the value would be
   - No time/not a priority
   - Our licensing partner is responsible for interaction with the HTA Authority

24. What are the key challenges for your company regarding compliance with HTA requirements? (multiple answers possible).
   - We don’t understand HTA processes and uses
   - It is not clear what decision criteria are used by our national HTA Authority
   - Difficult to recruit required number of patients
   - Identifying a comparator accepted as standard of care by HTA authorities (or reimbursement bodies)
   - Don’t know
   - Other (please explain)
     ____________________________________________________________
     ____________________________________________________________
     ____________________________________________________________

25. Has your National HTA Authority got any initiative to raise awareness and increase understanding of HTA requirements among SMEs?
☐ Yes (if so, have the activities helped you to use the opportunities with HTA? Please provide a brief explanation)

___________________________________________________________________

___________________________________________________________________

___________________________________________________________________

☐ No

☐ Don’t know

26. Have you been rejected by an HTA Authority when attempting to discuss potential end points relevant for reimbursement?

☐ Yes

☐ No, we were always welcome to discuss

☐ No, because we have not tried to discuss

QUESTION 27: ANY OTHER COMMENT

27. Please fill the box below if you have any other comment

___________________________________________________________________