

**Deerfield Institute -  
EuropaBio Report on  
REGULATORY AND HTA  
SCIENTIFIC ADVICE  
FOR SMALL AND  
MEDIUM ENTERPRISES**

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## *Introduction*

Phase III clinical trials are the last and vital development step before submitting products for approval, and while the costs for these are rising, their success rates are relatively low. Regardless of the resources poured into these costly and crucial trials, there is still a 50% failure rate at phase III, according to the UK's Centre for Medicines Research.

Despite this financial burden, companies, regulatory and HTA (health technology assessment) authorities are starting to work together at earlier stages of drug development in order to make drug development more efficient. This could eventually help companies find out what data the authorities need, thus leading to better designed clinical trials, and fewer drugs failing at the approval stage, or not being reimbursed.

To find out more about the current state of regulatory and HTA advice, and plans for the future, EuropaBio has partnered with the Deerfield Institute to carry out a survey through a series of interviews with companies, regulatory authorities, and HTA bodies. The interviews were held between 2013 and 2014 and this report synthesizes feedback from these interviews.

## *Key findings*

The findings of this survey suggest early regulatory scientific and HTA advice may help small and medium enterprises (SME) to better prepare and manage their clinical programs toward facilitating both regulatory approval and positive HTA recommendations. Despite agreement amongst all stakeholders that such interactions would be positive, obstacles to effective implementation exist for SMEs. As these companies may be inexperienced, the process can be perceived as lengthy, formal, and cumbersome, particularly as they often lack the resources of their larger peers. Both sides expressed the need to become more flexible in their interactions to increase both the number and variety, and possibly allow for SMEs to receive joint HTA and regulatory advice.

The below section summarises key findings of the survey grouped by stakeholder category.

### **The regulatory scientific advice: the regulators' perspective**

- Scientific advice can help companies develop robust clinical trials, improving the chance of approval and increasing the efficient use of resources
- SMEs have different issues and needs compared to larger companies
  - Companies are often less experienced
  - Clinical trial design is more critical
  - Regulatory authorities need to be flexible and pragmatic

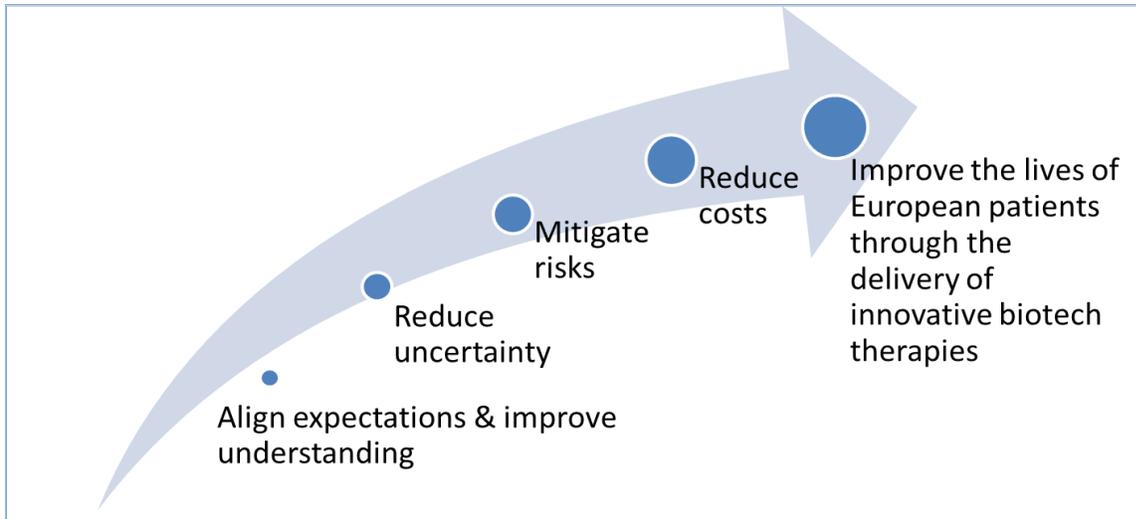
### **The HTA scientific advice: the HTA body's perspective**

- Seeking early HTA advice allows companies to check that their drug development program is on track to receive recommendations from the HTA bodies after approval
- Companies need to seek HTA advice earlier; it could also reduce development risk, and make best use of limited resources
- Seeking early advice improves transparency
- There are different types and levels of support available to SMEs
- Joint HTA and regulatory advice could have a major impact by optimizing the planning of clinical trials from both a cost and risk perspective
- Challenges include changes in mind-set, and the need for new skills – there is a need for communication and training
- It can be difficult to reconcile requirements from different country HTA bodies, while advice would ideally be consistent across the EU

### **The regulatory and HTA scientific advice: the companies' perspective**

- Companies with products at earlier stages are more likely to seek local regulatory advice at phase I and II, or use the EMA's innovation task force
- Seeking regulatory advice provides a first review of data, accesses expert validation and advice, keeps both sides up-to-date in cutting-edge research, and improves communication from both directions
- Challenges and obstacle to seeking advice can come from within the company, particularly when it relates to HTA advice
- SMEs are willing to engage in HTA advice activities because it can help them better understand HTA requirements and add new, relevant information in the choice of comparator(s) and/or endpoints
- Companies can find it hard to identify the right questions to ask, and find the process lengthy, formal, and cumbersome
- The advice given can be difficult for small companies to follow up, because of costs and resources
- There may not be enough opportunities for meetings and discussions
  - SMEs are looking for more support, recommendations and discussion – they want the regulatory and HTA authorities to be more of an active development partner
- There needs to be more consistency across authorities

**Figure 1. Regulatory and HTA advice activities: better outcomes and lower costs**



## 1. The regulatory scientific advice: the regulators' perspective

**Table 1: Interviewed regulatory agencies**

Name	Number of Employees	When did your institution start providing early regulatory advice?	Number of new products per year	Number of meetings a year	Number of officers and % of time
EMA	800	Informally CPMP 1996; formally in 1999	300	300 face-to-face meetings, including pre-submission and during procedure	10 medical doctors and pharmacists – 90% on regulatory advice; 7 secretaries – 90% on logistics; SAWP – 27 national experts plus network

### **EMA**

The European Medicines Agency (EMA), based in London, is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995, and has around 800 employees. These include medical doctors and pharmacists, secretaries and national experts who spend 50-90% of their time on regulatory advice. The EMA provides scientific advice on around 300 new products per year.

### 1.1. Why provide scientific advice?

Some drugs fail to receive approval, not because the drug isn't good enough, but because the development has taken the wrong path or the data simply do not fit into the regulatory authorities' formal requirements. Scientific advice can help companies develop robust clinical trials with more appropriate endpoints, eventually reducing risk and waste of resources.

**Table 2: Scientific advice and EMA approval (2006-2014)**

	N. of Medicines	Approval rate
<b>New Medicines</b>	371	74.9%
Scientific Advice	219	74.9%
Once	119	66.4%
Twice	57	82.5%
Three times	43	88.4%
<b>Oncology Medicines</b>	78	71.8%
Scientific Advice	54	70.4%
Once	28	64.3%
Twice	18	77.8%
Three times	8	75.0%
<b>ATMPs</b>	9	44.4%
Scientific Advice	8	50.0%
Once	6	33.3%
Twice	1	100.0%
Three times	1	100.0%
<b>Orphan Medicines</b>	109	67.9%
Scientific Advice	76	63.2%
Once	37	54.1%
Twice	25	68.0%
Three times	14	78.6%

Source: DI analysis based on EMA data

The Deerfield Institute analysed data from the EMA European Public Assessment Reports (EPAR) of 371 new drugs (excluding generics and biosimilars) reviewed from 2006 to mid-2014. The analysis was aimed at better understanding how frequently companies asked for scientific advice and whether scientific advice had a positive impact on EU approval. Sub-group analyses were done for oncology medicines (78 drugs in total), advanced therapies (nine) and orphan medicines (109).

Several caveats should be taken into consideration before drawing conclusions based on these data. For instance, neither SMEs' applications nor specificities of the scientific advice processes were examined in this analysis. The companies' questions, CHMP responses, or how companies addressed those responses were not taken into consideration. Another dimension not studied is the extent of innovation or underlying complexity of development programs. These aspects and others may play a major role in influencing drugs' approval. Another caveat could be that companies asking advice typically chose the questions to ask; having asked advice to EMA does not necessarily mean the company has asked advice on the most relevant issues. With the above caveats in mind, the analysis shows that drugs that received scientific advice at least once had the same average approval rate as the whole universe of new drugs (both **74.9%**, Table 2). Sub-group analyses for oncology, ATMPs and orphan drugs yielded similar results. Interestingly, companies seeking and having only one round of advice showed a relatively low approval rate (**66.4%**) for the universe of new drugs. Companies that had two or three rounds of advice showed well above average approval rates. For all new medicines examined here, companies that engaged in two or three scientific advice interactions had an approval rate of respectively **82.5%** and **88.4%**. Similar trends are demonstrated in each of the three subgroup analyses. Two or three scientific advice rounds may be an indication of earlier interactions with EMA during the drug development phase, where at second and third rounds companies can provide EMA feedback on changes in the development plan.

These data, while falling short of making firm conclusions, may be helpful in making some early comments:

- 1) The majority (**60%**) of companies asked for EMA scientific advice during the development of new drugs that underwent CHMP review between 2006 and 2014.
- 2) Seeking scientific advice is not sufficient alone to achieve a higher than average approval rate.
- 3) One scientific advice interaction does not seem to grant as much advantage in gaining approval compared to two or three scientific advice interactions

### ***1.2. How do regulatory authorities support small and medium companies, including biotechs, and why do companies ask?***

SMEs have different issues and needs compared to larger companies. Small companies tend to have less available funding, and thus less flexibility in terms of study feasibility. This constraint makes creating the right clinical trial design from the beginning particularly important. Smaller and younger companies often have less experience with regulatory issues. Here, the challenge is converting their innovative clinical and technical expertise to applicable regulatory science and approaches. Products emanating from these smaller and more innovative companies can in turn prove a challenge for the regulatory authorities as the products can involve novel modes of action or delivery routes.

To address these challenges, the EMA aims to be more 'hands- on,' flexible, and pragmatic with these companies. This could include reductions on fees, or access to face-to-face informal meetings, training, and mentoring.

## 2. The regulatory scientific advice: the SME companies' perspective

**Table 3: Interviewed companies**

Company	Focus	Selected products from clinical-stage pipeline
Ablynx <a href="http://www.ablynx.com">www.ablynx.com</a>	Discovery and development of antibody-derived therapeutic proteins for a range of serious human diseases including inflammation, haematology, oncology and pulmonology	Three products in phase I and three in phase II
Cardio3 Biosciences <a href="http://www.c3bs.com">www.c3bs.com</a>	Discovery, development and commercialization of regenerative and protective therapies for cardiovascular diseases	Cell therapy in phase III
ERYTECH Pharma <a href="http://www.erytech.com">www.erytech.com</a>	Encapsulation of anticancer therapeutic molecules into red blood cells	Phase III in ALL, phase II/III in AML
Genmab <a href="http://www.genmab.com">www.genmab.com</a>	Creation and development of differentiated human antibody therapeutics for the treatment of cancer	Three projects in phase I and II, seven in phase III
Prosensa <a href="http://www.prosensa.eu">www.prosensa.eu</a>	RNA-based therapeutics to address unmet medical needs for patients with genetic disorders	One phase III under way, five phase I and II
Raptor Pharmaceuticals <a href="http://www.raptorpharma.com">www.raptorpharma.com</a>	Developing and commercializing life-altering therapeutics that treat rare, debilitating and often fatal diseases	RP 103 is in phase III development for the treatment of Huntington's disease
TiGenix <a href="http://www.tigenix.com">www.tigenix.com</a>	A stem cell therapy company	Adipose stem cell products – one in phase I, one in phase II, one in phase III
Transgene <a href="http://www.transgene.fr">www.transgene.fr</a>	Discovering, developing and manufacturing targeted immunotherapies for the treatment of cancer and infectious diseases	One product in phase III and three products in phase II
UniQure <a href="http://www.uniqure.com">www.uniqure.com</a>	Gene therapy – single treatments with potentially curative results	Four projects in clinical trials

### ***Ablynx***

Ablynx has European revenues of €30 million from licensing, and its costs – mostly in Europe - are €60 million on operating costs and €50 million on R&D. Of its 280 employees in Europe, 0.1 FTE is focused on HTA (with additional outsourced when working on out-licensing) and three-to-eight FTE on regulatory issues. A number of nanobody products have received regulatory advice. For more information, see Appendix.

### ***Cardio3 Biosciences***

Cardio3 Biosciences R&D costs were €6.5 million in 2012, €6 million of which were in Europe. Of its 52 employees in Europe, one part-time outsourced equivalent is focused on HTA (with a CRO) and two employees (only one full-time) outsourced on regulatory issues. Two products have received scientific advice. For more information, see Appendix.

### ***ERYTECH Pharma***

ERYTECH Pharma has not disclosed its revenue or costs. Of its 41 employees, two are focused on regulatory issues, with two or more consultants as required. No employees are dedicated to HTA work. The company has received regulatory advice for GRASPA, a cancer therapeutic; its partner is taking care of HTA matters. For more information, see Appendix.

### ***Genmab***

Genmab's revenues are €65 million, with operating costs of €80 million and R&D costs of €71 million. Genmab has 167 employees in the EU and 175 overall. Of these, two employees are dedicated to regulatory issues, with two outsourced, and no employees are focused on HTA issues. So far, it has not received HTA or regulatory advice. For more information, see Appendix.

### ***Prosensa***

Prosensa has no product revenues and variable licensing revenues. Its operating costs were €18 million in 2012, with €15 million in R&D costs. Former partner GlaxoSmithKline was responsible for HTA activities. At the time of the interview, Prosensa had 2.5 FTEs (of a total of 90 employees) working on regulatory issues, with additional support from GSK. Prosensa has received regulatory advice on four of its products. For more information, see Appendix.

### ***Raptor Pharmaceuticals***

Raptor had no revenues to report in 2012, and costs were not disclosed. The company outsources headcounts for HTA and regulatory issues (one for HTA and 0.4 for regulatory). No advice has been sought. For more information, see Appendix.

### ***TiGenix***

TiGenix has not disclosed information on finances or employee numbers. At the time of interview, it had 0.5 FTE outsourced employees working in HTA issues and three internal employees in the regulatory field. TiGenix has sought regulatory advice for three products. For more information, see Appendix.

### ***Transgene***

Transgene's EU revenue in 2012 was around €10 million, with operating costs of €50 million and €30 million in R&D investment. Transgene had 260 employees, with one dedicated to HTA issues (plus consulting contracts) and seven dedicated to regulatory affairs (plus one-to-two outsourced). Transgene has received both regulatory and HTA advice. For more information, see Appendix.

### ***UniQure***

UniQure has reported its revenues as zero, with no disclosures on costs. At the time of interview, it had 115 employees, and used two outsourced individuals for HTA issues. Six employees are dedicated to regulatory issues, and UniQure had at least one FTE per year on a contract basis. For more information, see Appendix.

## ***2.1. How companies use the regulatory process***

A number of the companies interviewed have sought scientific advice from the EMA as part of their product development process, generally from the end of phase II or later. Companies with products at earlier stages are more likely to seek local advice at phase I and II, or use the EMA's innovation task force.

## ***2.2. The benefits of seeking regulatory scientific advice***

Seeking regulatory advice has a variety of benefits, according to the companies interviewed:

- Provides a first review of the clinical and preclinical work, with an expert's perspective and validation
- Helps design and validate relevant and effective trials, which can reduce development risk, and avoids later issues by defining useful clinical endpoints and selecting comparators
- Gets companies thinking about the approval process much earlier
- Smooths the path to approval by gaining input from experienced regulators, ensuring that overall product development is in line with regulatory expectations for product registration – this can also be useful for discussions with regulators in individual countries
- Allows companies to understand the concerns of the regulators related to study design and target indications, and helps both sides to establish early relationships and create trust
- Allows companies to keep up-to-date on sensitivities and potential concerns, such as emerging quality-related concerns, new test criteria or novel analysis methods
- Provides opportunities to get input on manufacturing processes, particularly important for complex products that involve newer technologies, such as genetic engineering
- Allows regulators to become familiar with new product approaches and modes of action

### ***2.3. The challenges with seeking regulatory scientific advice***

Companies seeking early regulatory advice face a range of challenges, from getting internal buy-in, creating the most useful questions to ask, and building the right data sets.

- Within companies, it is not always easy to convince senior management that seeking advice is a good approach. And once in place, managing the process and translating advice into actions can be a challenge
- The EMA can look for specific rather than open questions, and so it can be difficult for companies to define the right questions when seeking advice, particularly at early stages of development
- Compared with local advice, the EMA process can be lengthy, formal, and cumbersome, and EMA's approach can be perceived as conservative and inflexible. This adds to the burden of preparing documentation, questions, and justifications, all of which contribute to lengthening the process, which is particularly challenging for SMEs, who have fewer resources
- Sometimes the EMA's responses are not sufficiently clear, and local authorities and the EMA may ask for different things
- Regulatory authorities can ask small companies to carry out processes that are very challenging, potentially taking resources away from other scientific research. Additional requirements at an early stage can also meaningfully increase development costs and timelines, which has a major impact on SMEs, and could even force a company to abandon development projects or even go out of business
- While SMEs and orphan products are treated as special cases, the costs can be high for non-orphan products and non-SME companies, and the approach is not always appropriate for ATMP products
- Meetings with regulators are not always granted, so there may not always be an opportunity to have a face-to-face dialogue. Written procedures are instead more easily available, which offer limited opportunities to build relationships and to discuss and exchange ideas
- There are not enough opportunities for discussion with the EMA reviewers – apart from the pre-submission meeting which is a good venue for informal exchange, the official “oral explanation meeting” remains very formal with no opportunity for discussion of questions, and written procedures
- Companies working in new therapeutic areas may have to address many questions and comments from regulators, as the mechanism of action or disease area may be unfamiliar

### ***2.4. Regulatory advice: Needs and recommendations from the companies***

The EMA and other regulatory authorities need to address these challenges and concerns, in order to improve the process and encourage more companies to get involved:

- Companies, particularly those that are smaller or less experienced, are looking for support and recommendations that reach beyond the answers to specific questions rather than 'take it or leave it' advice

- Companies, including manufacturers, would like to have the opportunity for more discussion with regulators before final advice is issued
- Regulatory authorities should aim to be an active development partner
- Companies would find it useful to have one EMA contact for informal exchanges and advice
- A process similar to the FDA's breakthrough therapy designation (BTD) would be helpful, including support in technology development, which would help to create a favorable environment for breakthrough innovation
- The authorities need to have better awareness of ATMPs and orphan drugs, more expertise, and improved support in this area, for example a liaison officer expert in the field
- The authorities should move towards more consistency across countries and better harmonisation

***2.5. Regulatory advice: Needs and recommendations for the companies***

- Companies without the expertise in-house should work with consultants expert in the area
- Manufacturers should work with the EMA early in the process.

### 3. The HTA scientific advice: the HTA bodies' and SME companies' perspectives

**Table 4: Interviewed HTA and regulatory bodies**

Name	Employee numbers	When did your institution start providing HTA advice?	Number of new products per year	Number of meetings a year (2012-2013)	Number of officers and % of time	How many SMEs have you advised on how many products?
<b>AIFA</b>	380	2011	National In 2012: 1, 2013: 2 EMA In 2012: 3, 2013: 3 EUnetHTA In 2012: 3, 2013: 4	7-9	11 people, 20% of their time	4
<b>ZIN</b>	400	Tapestry: 2010-2011 EUnetHTA: 2011	EUnetHTA In 2012: 6-8, 2013: 8-10	6-10	6 people, 2% of their time	Mostly big companies
<b>EMA</b>	800	2010	In 2011:8, in 2012: 7, in 2013: 7	14-16	As regulatory	2
<b>HAS</b>	100-110 (HTA); >400 overall	2012	10	10	20 person days per project + co-ordination	1
<b>NICE</b>	Approx. 100	2009	Approximately 20 (2012)	20	4 technical + 2 admin full time + 2 external experts	n/a

#### **AIFA**

The Italian Medicines Agency (AIFA) is the Italian national authority responsible for both drug regulation and pricing-reimbursement. It has around 380 employees. Of these, 11 people (administrative, legal, statisticians, pharmacists, clinical, and health economics specialists) spend 20% of their time on HTA advice. AIFA provides HTA advice on 1-4 products per year.

#### **ZIN**

Netherlands National Health Care Institute (Zorginstituut Nederland; ZIN) manages the basic Dutch healthcare package; it is also responsible for encouraging improvements in healthcare quality and supporting education and training for healthcare professionals. It has around 450 employees of which 140 are involved in HTA and health care quality (~50% of FTE on HTA), and of these, six people spend two percent of their time on HTA advice. ZIN provides early advice on six-to-ten products per year through EUnetHTA.

#### **HAS**

The French National Authority for Health (Haute Autorité de Santé; HAS) was created in August 2004 to improve the quality of patient care, from assessment of drugs, medical devices, and procedures through publication of guidelines to accreditation of healthcare organizations and certification of doctors, to training in quality issues and information provision. HAS has more than 400 employees, with 100-110

involved in HTA activities. HTA advice takes up around 20 person days per project plus coordination, and provides advice on about 10 projects per year.

### ***NICE***

Set up in 1999, the National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care, including evidence-based guidance and advice, quality standards and performance metrics, and information services. It has around 600 employees and of these, two technical and two administrative staff work on HTA advice full time, with two additional external experts per project. NICE provides HTA advice on around 20 products per year.

#### ***3.1. Is there a need for HTA advice?***

Companies may have limited experience in working with HTA bodies, and may not have staff dedicated to HTA work. This has led some products getting marketing authorization but not being recommended by the HTA bodies because the data was not sufficient to establish the required added clinical and/or economic value.

In response to this gap between company dossiers and HTA bodies' requirements, HTA bodies have started offering HTA advice to help companies get clinical trial design right the first time and not waste their precious resources. Seeking HTA advice allows companies to check that their own drug development program is on track to receive positive recommendations from the HTA bodies after approval. It may also decrease the overall development program risk and minimize uncertainty by providing an opportunity to find solutions and fill gaps at an early stage. This would be to the advantage of all parties - from the company, regulatory authority, and HTA body to the physician, patient, and payer.

#### ***3.2. Experience so far***

Getting recommendations from the HTA bodies is a mind-set change for companies, and small companies particularly tend to be focused more on getting regulatory approval, meaning they do not seek advice until it is almost too late. This may be because of a lack of understanding of the importance of the HTA process, or issues with limited resources. According to NICE, there has been more demand for on-the-spot advice than its small team can handle. This could perhaps be mitigated by companies' better understanding the importance of the HTA processes and requirements specific to their drugs, ensuring that questions are specific and focused on HTA issues rather than on regulatory issues, and by planning further in advance.

The HTA bodies interviewed have reported that, although experience of HTA advice has been limited so far with SMEs, this has been a positive experience, with fewer problems than expected. They have found the companies involved to be focused, responsive and pragmatic.

### **3.3. Support to SMEs**

There are different types and levels of support available to SMEs:

- The EMA runs meetings every year that include sessions that explain the scientific advice (including HTA) process to SMEs
- NICE has seminars for pharmaceutical and medical technology companies available on its website, that have been created bearing small companies in mind
- NICE could also develop HTA training and seminars for SMEs, which could include MedTech and ATMP companies, and can create training to meet specific needs for SMEs or particular audiences
- According to ZIN, it would make sense to provide support and training at EU level

### **3.4. Working together: Regulatory and HTAs**

The limited available resources make it extremely important that clinical trials incorporate the requirements of both regulators and national HTA bodies, and having access to both at the same time would make SMEs' life much easier. To achieve this end, the EMA has been working closely with the HTA bodies in Europe since 2008.

The companies, HTA bodies, and regulatory authorities interviewed were positive about the idea of joint advice. Some companies strongly supported the concept, noting joint advice and common EMA and HTA guidelines would be game-changing, providing consistency across Europe, and improving the timeliness of the whole process.

The advantage of a joint approach is that it would optimize the planning of clinical trials from both a cost and risk perspective.

The multi-country and multi-agency approach would be more flexible in addressing country specific needs, and would eventually reduce the risk of failing to bring valuable innovation to market because of the inefficiencies of the system. At the same time, companies may face the risk of having to deal with conflicting advice from regulatory and HTA bodies.

### ***3.5. How companies work with the HTA bodies***

A number of the companies interviewed sought HTA advice. One company found the input was highly consistent where objectives and principles were concerned. The same company experienced some inconsistent input in data requirements from different agencies, for example in the level of details required, or in selecting comparator drugs. Discussions and advice on the blinding approach, patient demographics, HE (Health Economic) data requirements, and relevant endpoints were useful, and led to the removal of some irrelevant endpoints.

Some of the companies interviewed did not seek early HTA advice, because it was not available, was not appropriate, they were not aware they could, or because their partners were leading and addressing the HTA aspects. And for some companies, their focus was on the development process and they simply ran out of time.

Another company did not seek early HTA advice, based on past experience with a marketed product, and the inconsistencies in HTA advice between countries.

### ***3.6. Benefits for companies seeking HTA advice***

- Helps companies to set up trials with the right comparators, endpoints, and patient-related outcomes
- Helps align the development process and understand HTA needs at an early stage
- Improves transparency, by helping companies learn about HTA bodies' needs and expectations, and increasing HTA bodies' awareness of company pipelines and R&D plans
- With high cost treatments, early discussions will help companies understand the product's value from the HTA perspective
- Helps companies understand what payers need

### ***3.7. Challenges for companies seeking HTA advice***

- Companies lack HTA skills, and gathering HTA advice from a multitude of agencies seems like a complex and daunting process
- Communication with internal teams, such as clinical and regulatory groups, can be challenging, as HTA language and approaches can be very different to those accustomed to R&D. It is important to engage all internal stakeholders in discussions and convince them that there is a real need to adapt trial design to accommodate HTA bodies' requests
- Requests from different countries can be difficult to reconcile in the clinical program, especially for small companies

- In some cases, HTAs might not have the most appropriate approaches, processes and methodologies for ATMPs, and have less experience with these compared to the EMA
- According to two of the interviewed companies, HTA bodies have a reputation for being more bureaucratic than the EMA, and somehow lacking scientific expertise in particular when it relates to ATMPs or rare conditions

### **3.8. HTA advice: Needs and recommendations from the companies**

- The process needs to be less daunting and complex for SMEs
- The HTA evaluation process needs to acknowledge the unique characteristics of ATMPs, personalized medicines, rare and ultra-rare diseases
- HTA bodies need to be more consistent across the EU – a more coordinated HTA approach across Europe would be helpful, together with new accelerated approach processes
- HTA bodies should look at alignment with other stakeholders, including patient associations and clinicians
- HTA bodies need to better understand the science and technologies
- Companies' needs for support and training:
  1. EMA and HTA body mentoring activities
  2. SME training on the HTA process overall across Europe, country by country
  3. Training for R&D departments, so that they know what the HTA procedures and methods, especially in how HTA requirements could translate into changes in the development plan such as different endpoints, methods, and objectives, including ways to adapt clinical trial designs, processes and timelines
  4. Training, information and guidelines on disease-specific HTA requirements
  5. Joint EMA/HTA training for SMEs as well as for ATMP manufacturers

### **3.9. HTA advice: Needs and recommendations for the companies**

- Companies need to have clear understanding of HTA requirements for clinical trial design, such as safety and efficacy outcome measures, target population definition, the comparators, burden of illness, epidemiological data, and for certain countries the requirements of health economic data
- Companies should seek advice early during clinical development and use a consultant or set up a partnership if HTA skills are not available in house
- Companies need to invest time in training

## *Conclusions*

Seeking early regulatory and HTA advice has the potential to improve the chances of drugs making it through both the approval and HTA processes and onto the market, where they can change the lives of patients. While the scientific advice programs have made good starts, and have received positive feedback from the companies, there are still needs to be met, particularly in the areas of information, training and coordination.

## Appendix

**Table 5: Interviewed companies, EU Financials**

Company name	Revenues in Europe (global)	Operating costs in Europe (global)	Investment in R&D in Europe (global)
Ablynx	€30 million licensing	€60 million	€50 million
Cardio3 Biosciences	0	€6.5 in 2012	€6 million
ERYTECH Pharma	0	NA	NA
Genmab	(€65 million/ DKK485 million)	(majority of €80 million/ DKK601 million)	(€71 million/ DKK537 million)
Prosensa	No product revenues; licensing revenues €8 million in 2012	€18 million in 2012	€15 million in 2012
Raptor Europe	€ 0	NA	NA
TiGenix	NA	NA	NA
Transgene	€10 million	€50 million	€30 million
UniQure	0	NA	NA

**Table 6: Interviewed companies, EU operations**

Company name	Discovery	R&D	Commercial	Manufacturing
Ablynx	Y	Y	Limited	Development - in-house; Commercial - outsourced
Cardio3 Biosciences	Y	Y	Not yet	Y
ERYTECH Pharma	Y	Y	Not yet	Y
Genmab	Y	Y	Not yet	CMO outsourced (Europe)
Prosensa	Y	Y	Pre-commercial	Y
Raptor Europe	Y	Y	Y	Y
TiGenix	Y	Y	Y	Y
Transgene	Y	Y	Not yet	Y
UniQure	Y	Y	Y	Y

**Table 7: Interviewed companies, EU employees**

Company name	Number of FT (Full Time) employees in Europe (global)	HTA FT employees/resources	Regulatory FT employees/resources	R&D FT employees/resources
Ablynx <sup>1</sup>	280 (280)	0.1 (outsourced when working on outlicensing)	Internal: 2 senior + 6 support; Outsourced: depends on project	220
Cardio3 Biosciences	52 (52)	0.5 outsourced from CRO company	Internal: 2 Outsourced: 1	Internal: 12 External: 2
ERYTECH Pharma	40 (41)	0	Internal: 2 Consultants as required	Around 20
Genmab	167 (175)	None	Internal: 2 Outsourced: 2	Internal: 143 Also outsourcing in Europe
Prosensa	88 (90)	Not yet (GSK carrying out HTA for lead product)	Internal: 2.5	Internal: 70+ Also outsourcing
Raptor Europe	5 (60)	-	-	-
TiGenix	-	0.5 outsourced	Internal: 3	25
Transgene <sup>2</sup>	260 (260)	1 internal + consulting	7 internal + 1-2 outsourced	60 research and 20 development
UniQure	112 (115)	2 outsourced	At least 1	70 internal

<sup>1</sup> Ablynx had an EU SME status before 2012 and therefore relevant for this survey

<sup>2</sup> Transgene had an EU SME status before 2012 and therefore relevant for this survey

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Advancing Healthcare™

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