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Human Medicines Research and Development Support Division

Workshop report

Demonstrating significant benefit of orphan medicines: concepts, methodology and impact on access – 7 December 2015

1. Introduction

In December 2015, the EMA hosted a workshop to discuss the concept of significant benefit with regards to the European orphan legislation. This was the first public workshop on this topic since the introduction of the orphan legislation in 2000. The workshop brought together more than 200 representatives including European regulators, Health Technology Assessment (HTA) bodies, the pharmaceutical industry, patient representatives, health care professionals and academics. Also present were representatives from the Committee on Medicinal Products for Human Use (CHMP), the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), the Scientific Advice Working Party(SAWP), and the Committee for Advanced Therapies (CAT). A further more than 400 participants across 32 countries worldwide accessed the event via a live webcast.

The meeting was opened by Prof Bruno Sepodes, Chair of the COMP and Dr Jordi Llinares, Head of Product Development Scientific Support at the EMA who welcomed the participants and set out the goals of the meeting. The objectives were the following:

- To explore concepts on demonstration of significant benefit of orphan medicines over existing treatments;
- To discuss existing methodologies for significant benefit based on clinically relevant advantage, including indirect comparison methods, and for major contribution to patient care, including patients' inputs, and how they could be applied to the demonstration of significant benefit at marketing authorization;
- To discuss the impact of significant benefit on HTA assessment, pricing decisions, and access to orphan medicines;

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Legal basis of orphan medicines in the EU

The following slides present the current legislative documents in the EU relevant for orphan medicines.

Regulations, guidelines and recommendations

- Regulation (EC) No 141/2000 on Orphan Medicinal Products
- Commission Regulation (EC) No 847/2000
- Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)
- Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another (ENTR/6283/00 Revision 4, 2014)
- Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C 178/02)

Definition of significant benefit

Article 3(1)b in Commission Regulation (EC) 847/2000 states that in the case where satisfactory method(s) of diagnosis, prevention or treatment of the condition exists, the sponsor has to establish 'that the medicinal product will be of significant benefit to those affected by that condition'.

Significant benefit is defined as 'a clinically relevant advantage or a major contribution to patient care.'

2. Session 1: Significant benefit concepts and experience

2.1. Significant benefit: origins and experience up to date

This topic was introduced by Prof Kerstin Westermark (COMP and SAWP member), who outlined the fundamentals of the orphan legislation and discussed the background and concepts of "significant benefit" within the legislation. Significant benefit needs first to be demonstrated at the initial orphan designation (OD) when it can be based on assumptions, since most products at the time of OD will be at preclinical or early clinical stage of development. Subsequently, significant benefit needs to be confirmed at the time of marketing authorization (MA). The review of the orphan status at the time of MA is performed by the COMP according to a timeline that is parallel with the CHMP assessment, and a final decision on the maintenance of orphan status is made by the COMP after a CHMP positive opinion on granting a marketing authorisation. The Sponsor has to provide a report to the COMP containing data supporting the maintenance of orphan designation criteria, based on which the COMP will assess if the orphan criteria still hold.

Importantly, significant benefit has to be demonstrated in comparison with all products authorised for the condition at the time of MA, including those that were authorised during the time period between OD and MA. If there is insufficient evidence to support the claims of significant benefit at the time of MA, the product can still be authorised but without the orphan status. It was also clarified that significant benefit has to be demonstrated at the time of MA irrespective of the type of MA (e.g. there are no special provisions for a "conditional" significant benefit in cases when the product receives a conditional MA).

Prof Westermark concluded stating that it is responsibility of the sponsor to make sure that there is sufficient evidence for the COMP to confirm significant benefit.

2.2. Clinically relevant advantage and major contribution to patient care

Dr Laura Fregonese (EMA) explained under which circumstances significant benefit has to be demonstrated. Significant benefit has to be shown if "satisfactory treatments" are available for the particular condition and currently that is the case for more than 70% of all designated orphan products. The definition of satisfactory treatments includes medicines with a centralized or national marketing authorization in the EU, and additional non-pharmacological methods that are part of the best standard of care e.g. surgical techniques.

Furthermore she explained the conceptual grounds for significant benefit which can be based either on "clinically relevant advantage" and/or a "major contribution to patient care". These two main areas can be further broken down in sub-categories that constitute different grounds on which significant benefit can be granted, e.g. to medicines that show a therapeutic benefit in patients relapsing from previous treatments, or additional benefits in combination with some of the currently authorized products for the given condition. Dr Fregonese concluded with a discussion on the challenges of assessing significant benefit, that can be difficult to establish in conditions where there are several products authorised, and may require the comparative discussion with a relatively large number of products. Similarly it may be challenging to generate the appropriate data to establish a major contribution to patient care, as claimed advantages of e.g. a new formulation or administration route need to be substantiated with data. Early engagement with EMA protocol assistance is strongly recommended in order to obtain guidance on the maintenance of significant benefit at MA.

2.3. Questions and discussion

The questions were moderated by Mrs Lesley Greene (Vice Chair of the COMP).

The issue of conditional marketing authorization (CMA) and unmet medical need was questioned in relation to the significant benefit. It was questioned how there can be a CMA in an area of unmet medical need but potentially no demonstration of significant benefit. Prof Westermark emphasised that the two pieces of legislation are different and that there is currently no "conditional significant benefit". She also highlighted the importance of discussing significant benefit during protocol assistance[1].

A further topic raised was 'what is relevant with regards to significant benefit'. It was mentioned that patients may have different opinions of what is relevant with regard to Significant Benefit and whether there may be better ways of capturing their views. Dr Fregonese responded that decisions on the most relevant endpoints, including those capturing patients' views should stem from discussion and collaboration not only between regulators and industry, but also with academia and patients that have

[1] **Protocol assistance** is the special form of scientific advice available for companies developing designated orphan medicines for rare diseases.

to work together to generate the data and work towards validation of new outcome measures to be used for regulatory purposes.

There was also the expression of a wish to have more details on the significant benefit discussion of the COMP, published in the EPAR. This question was answered by Dr Llinares who mentioned that there is information published in the minutes of the COMP and in the Public Summaries of Opinions (PSO). However, the information provided is limited, and it was taken as an action point to investigate how this information could become more accessible.

3. Session 2: The significant benefit of oncology products

3.1. Significant benefit of oncology products at marketing authorization: the COMP experience

Dr Frauke Naumann-Winter (COMP) presented data and statistics from orphan designations in the oncology field (years 2000-2015), which constitute almost half of all designations and of the authorised orphan medicinal products. The significant benefit of oncology products at the time of MA is mainly based on improved efficacy of the new product in patients relapsing from previous treatments and/or in combination with the currently authorized products. Major contribution to patient care and improved safety are rarely used, mainly in combination with improved efficacy to establish the significant benefit.

Dr Naumann-Winter highlighted the importance of protocol assistance for sponsors to prepare for demonstration of improved efficacy over several products by direct or indirect approaches. This should take into account the pre-treatment history or the identification of subgroups unresponsive to authorised treatments. The exclusion of certain treatments in control groups or as combination treatments should be carefully considered. Examples of “ideal” settings and challenging cases of significant benefit of oncology products were presented and discussed. As part of the discussion it was also highlighted that endpoints should reflect tangible benefits taking into account the specific disease setting. The discussion on what is tangible and relevant in the setting of the significant benefit of oncology products is ongoing, and was one of the objectives of the afternoon breakout session 2. It is also evident that a claim of improved safety is especially difficult to be accepted, as at the time of MA generally only limited data on the safety profile of a new medicine are available. Dr Naumann-Winter concluded that due to the heterogeneity of oncologic conditions and the pharmacological treatment, a case-by-case approach for maintenance of orphan designation is required.

3.2. The ESMO-MCBS Clinical benefit scale of anti-cancer therapies

Prof Richard Sullivan (King’s College) reflected on his personal views as to why the ESMO-MCBS was created and how it can be used. The cost of cancer care is increasing and one of the driving forces of it is the cost for medicines. The expenditure range on medicines as a percentage of the total health care costs is varied, and has no correlation with actual outcomes. After briefly summarising the way the scale can be used he concluded on the following:

- The ESMO-MCBS is a tool for assessing whether a ‘valid trial’ has produced a ‘clinically meaningful endpoint’ as defined by a set of European medical oncologists and statisticians.
- It is not about ‘true value’ or more general value estimates, but more about the clinical value as assessed based on the methodology created by ESMO experts.

- As this scale can be used at any stage, and repeatedly over the life cycle of a product, i.e. also when post approval studies results become available, it has the possibility to take into account the evolving generation of evidence on the benefit/risk balance of oncology products.
- It is currently unclear what interface the ESMO-MCBC scale may have with the HTA assessments and aims.

3.3. Questions and discussion

The questions were moderated by Ms Kristina Larsson (EMA).

One question was if there will be continued work on the assessment process with other solid cancers apart from the ones reviewed until now. Prof Sullivan answered that indeed there will be. The ASCO scale includes value assessments, and the analysis methodology is different; however the conclusions so far are similar. Complex trial designs are difficult to put in this scale though.

A further question was if the incentives for developing orphan products are still attractive enough. Prof Sepodes considered that that was the case, since it gives the possibility to companies developing orphan drugs have the possibility to apply for EU and national funds, and to profit from very generous fee reductions for all EMA procedures.

A question was posed to Prof Sullivan if the COMP and CHMP should be stricter in their evaluation. Prof Sullivan considered that the regulatory process is focused on delivering an opinion on whether there is sufficient evidence of efficacy and safety for a new medicine to be licensed, which is fine. The drugs coming through the regulatory process have demonstrated an effect usually in one pivotal clinical trial. Whether these drugs will confirm this effect in the long run in clinical practice with more heterogeneous patient population remains to be shown, and needs to by systematically/repeatedly assessed. Following this there was a concern that if 40% of trials are not delivering fully conclusive results, are there any tools to be used at the stage of protocol assistance to limit the patient and resources 'waste'? Prof Sullivan did not think that was the case currently.

One question focused on if there is a higher hurdle for proving significant benefit when several products are authorised for the same condition, and how to tackle products that are authorised but not used.

Dr Naumann-Winter answered that not only approval but also treatment guidelines are important for the COMP when taking a decision on what the best comparators would be. The challenge of establishing significant benefit at the time of review not only depends on the number of products, but also on the effect sizes observed and the overall strength of evidence of the totality of the direct and indirect comparisons.

4. Session 3: Stakeholders' perspective on significant benefit

4.1. HTAs/payers

Mr Niklas Hedberg, (Dental and Pharmaceuticals Benefits Agency, TLV), explained the HTA assessment process and provided his views on the benefits of a new product vs old products, especially focusing on which comparator(s) to use during clinical development. In the nature of the HTAs the cost of a product comes into play and if a company is applying for a premium price, the company must prove that the new product has a "significant" benefit, also defined "added value" compared to the existing

therapies. If no such added value can be proven for the new product, a higher price may not be approved.

Mr Hedberg went on to discuss indirect comparisons which may be used when head to head studies comparing the new and the old therapy are not available. He emphasised that the appropriateness of performing indirect comparisons must be adequately justified, should allow evaluation of the transitivity assumption, and include sensitivity analyses.

4.2. Industry

Dr Adam Heathfield, (Pfizer /EFPIA/EuropaBio), started out by saying that in general industry values the Orphan Medicinal Products Regulation and how it currently works. With regards to significant benefit, industry is looking for an environment that properly balances two issues: 1) Incentives to be first *vs* incentives to continue to advance knowledge and care; and 2) Data collected prior to approval vs data to be collected post-launch. Delivering data that is meaningful to everyone can be far from easy in particular in rare diseases when randomised controlled trials can be unfeasible due to small patient population, lack of equipoise, no alternative treatments, or outcomes occur in the distant future.

Dr Heathfield mentioned the benefits of indirect comparisons but cautioned that the choice of methodology is context specific, and heterogeneity is a big problem. Indirect comparisons introduce less uncertainty when study populations, end points, study duration, and treatment settings, are sufficiently homogeneous. Furthermore he questioned what conclusions should be drawn if indirect comparison shows no benefit. Relative efficacy may not always be the only option but considerations like e.g. additional options in oncology treatment pathways or dissimilar interventions or target populations within a disease (mutation-specific vs all patients) could also be considered.

Dr Heathfield concluded by stating that companies are optimistic about new options to tackle some rare diseases in an even more meaningful way than in the past. But he also mentioned that the concerns from industry are about bringing HTA questions and evidence standards into regulatory framework as the context and consequences are different. Furthermore, higher evidence hurdles and more regulatory risk are likely to limit investments in research that could deliver incremental but important benefits to patients.

4.3. Patients

Mr Yann Le Cam (EURORDIS), opened his presentation by challenging whether the significant benefit assessment of orphan drugs was still required since we now have HTA bodies that assess relative effectiveness which was not the case when the Orphan Drug Regulation came into force 15 years ago. Also, with the current move towards adaptive pathways, regulatory flexibility and seamless approaches following the continuum of evidence generation for new products, the assessment of significant benefit at one single point in time is not always compatible with this new way of assessing data. Mr Le Cam continued to say that a mechanism of post-marketing re-assessment of the significant benefit would be needed but that is not foreseen in the regulation, although it would allow more flexibility without hampering the value of the orphan status.

Mr Le Cam also discussed how he thought the assessment of significant benefit could be amended to fit the new requirements. He advocated for more external experts and patients to be part of the significant benefit discussions at the time of MA. He also recommended collaboration with HTAs via EUnetHTA and supported previous speakers in the importance of making the reports of the COMP assessment publically available.

4.4. Questions and discussion

The questions were moderated by Dr Laura Fregonese (EMA).

The first question was to Mr Hedberg regarding if there were any specific rules for HTA for rare diseases. Mr Hedberg answered that the Swedish HTA does not distinguish between medicines with an orphan status and medicines or interventions targeting small patients populations of any kind when it comes to the methodology for assessment. Furthermore they have not decided yet on a specific decision making framework for rare diseases as opposed to more common ones.

An additional question was on the possibility of harmonising the HTA assessments over Europe. Mr Hedberg did not foresee at present a possible alignment between HTAs in EU as budgets are separated. However, the methodology for assessment could be harmonized.

Mr Le Cam was asked if a specific time point when orphan status needs to be confirmed was required. Mr Le Cam said that the intention of the legislation was to drive investment and that the confirmation of significant benefit is not needed in the same way today due to the HTA. He was of the opinion that if significant benefit is assessed too early in relation the level of evidence on a medicine, assessment may become a barrier to the development of orphan products. He also said that if there are no changes in the new EC Notice with regards to the possibility to reassess significant benefit it would be better to decrease the burden of evidence at the time of MA for significant benefit.

Prof Westermark stated that the COMP would like to involve more patients and external experts but that one of the major hurdles for this is the current EU system of assessing conflict of interest. She said that the COMP would have more experts if the rules were less strict. Prof Westermark also supported contribution from EUnetHTA in the COMP.

A final question was posed to Mr Le Cam on his view of the prices and access to patients of orphan drugs vs if the product was not orphan. Mr Le Cam answered that there is no evidence that the fact that there is an orphan drug vs non-orphan actually results in a higher price. The price is set during negotiation and the only measure to bring it down would be greater collaboration between payers in EU.

5. Break-out sessions

The break-out sessions discussed a number of issues previously specified. The groups concluded and presented their views to the plenary. These conclusions will be further discussed by COMP and cannot be understood as the official EMA/COMP position.

For each break-out session the participants had been sent specific questions one week in advance of the meeting to be able to prepare for the discussions.

5.1. Breakout session 1: Methodological tools for indirect comparisons: which use for significant benefit?

Moderators: Dr Andrew Thomson (EMA) and Dr Phillippe Motte (Abbvie)

The group discussed the methodological tools and challenges of using them, focusing on 5 key areas:

- What are the specific methodological challenges regarding rare diseases and orphan drugs in demonstrating significant benefit? What strategies can be proposed to maximize the information from sometimes limited data sets?

- What additional sources of data outside of the RCTs that support marketing authorization, if any, may provide a sufficient level of evidence to be reliably integrated into comparisons to the purpose of demonstration of significant benefit at the moment of marketing authorization?
- Assuming a positive benefit risk has been demonstrated, can the significant benefit process rely on the similar methodologies and type of data as the HTA assessment of clinical value? Could they apply the same evidence standards and benefit demonstration? What factors might affect the acceptability of this?
- What factors can influence whether indirect comparisons provide enough robustness to demonstrate significant benefit? Are these diseases specific and/or methodology specific? Is the time the comparison is being made important?
- In some instances, MAAs from different Companies in the same indication are submitted close together and the demonstration of significant benefit needs to take them into account at the same time. How can Companies go about comparing data when only partial data is available? How can other comparators be integrated into the discussion? What is a reasonable expectation of evidence that can be delivered in these circumstances?

For the first point, drift over time in response was highlighted as a key challenge, as well as heterogeneity of the patient population, which may pose bigger problems in rare diseases due to the already small numbers of patients enrolled in clinical trials. Obviously rarity is per se always a challenge but this should not prevent planning double blind RCTs when possible. In some, more prevalent rare diseases, trials with up to 1500 of patients have been possible. On the other hand, regulatory bodies have always been flexible in terms of data requirement in cases of very rare diseases (e.g. when only tens or hundreds of patients are affected around the world). A publication of NORD (National Organization for Rare Disorders) describing the level of evidence (quantum of effectiveness) based on which the FDA authorized all the existing orphan medicines in the US, was cited to address this point.

Regarding sources of data outside randomized clinical trials, registries were discussed in depth, including EMA initiatives such as the cross-committee Registries Task Force pilot projects. Benefits of registry data that were identified included their usefulness for endpoint definition, protocol development, patient recruitment and generating real world evidence. In this respect the importance of collecting information on the natural history of rare disease was highlighted. Concerns were raised that getting access to data from industry may be problematic, and funding for registries may run out before relevant data have had the chance to be generated. In addition there is still at present a significant heterogeneity across registries in the quality of the data collected, and furthermore the outcomes of interest for regulatory purposes may not be measured at all in registries already existing that had been created for different purposes. Access to clinical trial data, either through academic collaborative projects, industry publishing their own data, or in the future through regulatory authorities was highlighted as an important area for further consideration.

In terms of consistency of methodology across regulatory and HTA bodies, it was clear that there is no single solution, and that a case-by-case basis is currently used. For the factors that influence the robustness of comparisons, the challenge is ultimately for small treatment effects and small samples – a large treatment effect is always easy to interpret, even in rare diseases. A clear message was to focus not just on data but on trial design to get as much relevant data as possible. No clear solution exists for the challenge of providing sufficient data for comparison in the case of MA submissions of products temporally close together and this remains a challenging area for the establishment of significant benefit.

5.2. Breakout session 2: Significant benefit of oncology products: what is significant?

Moderators: Dr Pauline Evers (COMP member and Patient Representative) and Dr Paolo G. Casali (Istituto Tumori, Milano)

- It was considered that a case-by-case approach on what is necessary to confirm significant benefit will usually be needed for cancers, as the spectrum of disease is very wide and reaching from extremely rare conditions to less rare ones. Also the phase of disease where the treatment will fit (e.g. end-stage metastatic disease, adjuvant setting) influences the requirements for significant benefit with respect to comparative treatments and or the magnitude of the benefit.
- Apart from overall survival which was the preferred endpoint, surrogate endpoints were considered relevant for the determination of significant benefit, usually in the cases when they are used also as endpoints for the MA. No general rule can be defined when to use which endpoint. In tumour types with slow natural course of disease Progression free survival (PFS) or even durable response rate (RR) might be the better endpoint.
- If surrogate endpoints are used it is expected that they should be confirmed with a harder endpoint such as OS or PFS. The problem in this case is, that the review of the orphan status is done only at time of the initial marketing authorisation.
- When assessing OS or PFS, not only the median should be considered. Interpretability of the totality of the data including the censoring pattern and the maturity of the data needs to be addressed. A small group of patients with very long OS or PFS can contribute to the overall significant benefit for a product.
- In extremely rare cancers very limited data might be acceptable..
- The ESMO and ASCO clinical benefit scales are taking the natural course of the disease into account. This leads to the idea that e.g. 3 months additional benefit in OS or PFS in a disease with a bad prognosis (e.g. metastatic pancreatic cancer) is valued more than the same 3 months in a disease with a better prognosis (e.g. metastatic breast cancer). Taking this idea on board a percent increase in PFS or OS HR might be a better way of assessing significant benefit as compared to a numerical increase. This idea of basing the evaluation of the significant benefit on the relative rather than the absolute survival needs further considerations.
- There was a consensus in the group that the magnitude of benefit for rare cancers as compared to non-rare cancers should not be different, but the level of certainty (e.g. due to limited amount of patients) may be lower. The magnitude of response might also be valued differently for a first-in-class product as compared to a second-in-class.
- There was also a conclusion in the group that protocol assistance / scientific advice is a useful tool to agree on the optimal development of a product in a distinct condition.

5.3. Breakout session 3: Patient preferences and PROs in significant benefit

Moderators: Dr Daniel O'Connor (COMP) and Dr Andrea Beyer (Actelion)

The group discussed a number of topics including the need for consistent use of terminology, the settings when data are required and the barriers to collecting good data in the rare disease setting, with proposals for some potential solutions:

- The session was opened by Lesley Greene (COMP Vice-Chair and patient representative), who introduced the topic from the patient perspective, presenting views on major contribution to patient care, patient reported outcomes and patient preferences. Mario Ricciardi (COMP Member and patient representative) concluded the presentation with analysis of cystic fibrosis outcomes and preferences work carried out by Cystic Fibrosis Europe.
- During the discussions, it was agreed that the consistent use of terminology was of importance with regards to patient preferences and Patient Reported Outcomes. Although both have a different focus they were considered to be complementary
    - A PRO includes any outcome evaluated directly by the patient himself or herself and is based on patient's perception of a disease and its treatment(s)
    - Patient preferences in general are an expression of value for alternative options after informed deliberation of the potential risks and benefits
- One of the areas of discussion was is there such a thing as an "obvious" improvement/ benefit for the patient? In this regard, can it be determined under which circumstances robust data are required to demonstrate significant benefit, and are there examples where the benefit to the patient can be considered as 'self-evident'?
- It was discussed that patient data are normally collected in clinical trials and these do not necessarily reflect the real world setting. How should we collect and manage the heterogeneity of this data, and if outside clinical trials, what are barriers for integrating data from different sources and concluding on the effects. There were also views that patient health literacy plays an important role and that the correct tools in the rare disease setting are a key component
- In terms of how to overcome these challenges and what the potential solutions might be, members of the breakout group proposed that:
    - COMP could more proactively ask for PRO/ patient preference data or other methods to incorporate patients' views at protocol assistance at the EMA's Scientific Advice Working Party;
    - Sponsors should be encouraged to make more use of the EMA's Qualification of novel methodologies for drug development in relation to patients' reported outcomes and other methodology to capture patients' views;
    - There was a need for an early patient led drug development strategy, with a combined industry-regulatory-HTA-patient view;
    - Drug developers and patient groups should consider better use of technology for capturing the patient voice, e.g. using internet forums of patients discussing their experiences as potential source of data.

6. Conclusions

The workshop brought together more than 200 representatives from many interested parties in the orphan medicines field. The large participation in person and via broadcast confirmed the importance and interest in multi-stakeholder discussions on this topic. Even though this was not a consensus seeking meeting it was very encouraging to see different stakeholders, who are independently looking at related issues, coming together and sharing the knowledge and views.

The full day of talks and discussions covered the concepts and the many challenges in demonstrating significant benefit of orphan medicines over existing therapies. The existing legislation requires the orphan designation to be confirmed at the time of first marketing authorisation in a new orphan condition irrespective of the type of MA. The methodology of demonstrating and assessing significant benefit is therefore crucial.

A key “take home” message was the heterogeneity between orphan medicinal products requiring a case-by-case approach in data generation and assessment. Significant benefit should always be supported by data to substantiate claims ('self-evident' is not an acceptable ground even in case of major contribution to patient care), and such data generation should be prospectively planned. In this respect engagement with EMA protocol assistance is strongly recommended particularly in “crowded” and competitive therapeutic areas such as oncology.

It was of interest to understand the heterogeneity among HTA bodies with regards to handling and assessing orphan designated drugs. The scenario appears heterogeneous in Europe in the way the assessment of medicines is done with regards to relative efficacy/effectiveness. One way to facilitate patient access decisions could be to harmonize the methodology for HTA assessment across the EU. It was argued by industry that higher evidentiary standards, both at the regulatory side when significant benefit is assessed at MA, and potentially by HTA under harmonized requirements could limit investments in research that might otherwise deliver benefits that while incremental are nevertheless perceived as relevant by patients.

Increased transparency with regards to the COMP assessment of the significant benefit would be much appreciated by all stakeholders.

The breakout sessions allowed for more in-depth and informal discussions of the three areas and provided a variety of topics and views to be carried forward for future actions both for regulators and other stakeholders.

7. What next?

The regulators will aim at providing more public information with regards to the grounds of the COMP decisions, especially during the review of the orphan criteria at marketing authorisation.

Several actions are covered in the COMP work plan for 2016, e.g. COMP has created an ad hoc working group dedicated to providing guidance on the requirements for establishing significant benefit, including discussing the methodology for generating data for significant benefit at the stage of protocol assistance.

In the coming year the COMP will publish an article on significant benefit, and a revision of the “Recommendations on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation” (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003778.pdf) is also foreseen, but will await the outcome of the finalisation of the Notice,

in order to provide more supportive regulatory guidance to those developing medicines for rare diseases. The outcomes of the discussions held during the workshop will inform these projects.

The EMA Orphan office and the COMP will continue to monitor and participate in the discussions and consensus on the use of methodology for indirect comparisons and for studies in small populations. Some EU funded projects are ongoing in this direction (e.g. IMI IDEAL, ASTERIX and INSPIRE) which could inform future decision making.

Experience and discussions with HTA bodies are also considered relevant to inform future decisions on regulatory requirements in the area of significant benefit. In this respect a more consolidated approach of HTA bodies to orphan medicines would facilitate a continuum in the assessment and perception of the value of significant benefit along the whole life-cycle of orphan medicines.

A very important part of future activities is around patient input in the decisions on significant benefit. In spite of being highly desirable, the direct involvement of external patient experts in the COMP decision making is still limited. However future ways to involve patients more frequently will be actively explored and this is also an objective in the COMP work plan. EU funded projects are also ongoing with regards to patient preferences and patient reported outcomes.

EMA invites all stakeholders involved in the development of medicines for orphan diseases to continue identifying the challenges and suggesting solutions that can speed up the processes related to significant benefit assessment so that they can be accessed by those who need them more swiftly.