WORLD ORPHAN DRUG CONGRESS EUROPE

2023 SUMMARY

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Remap

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World Orphan Drug Congress Europe 2023

Remap Consulting joined over 1,200 other delegates from pharma, biotech and Payers/HTA's, in attending the largest and most established orphan drugs and rare disease meeting of its kind across the globe, in Barcelona, Spain from 30th October – 2nd November 2023.

Our report summarises some of the plenary sessions and parallel tracks that took place during the conference.

Keynote Sessions Overview

Are we ready to implement EU HTA in 2025? The future of ATMPs and OD availability

One of the first speakers at the World Orphan Drug Congress Europe 2023 was Dan Feldman of Eversana. His keynote session discussed how the industries' readiness for EU HTA couldn't be addressed with a "yes or no answer".

The Discussion

In the keynote panel discussing whether the EU HTA was ready for implementation in 2025, Dan Feldman, General Manager at Eversana, begun the discussion with the statement that "it is not a simple yes or no answer". To elaborate on the hurdles for the EU HTA from Europe as a whole, the panel discussed challenges faced in individual nations in the EU and how these challenges may be shared with other nations.

Diane Kleinermans, President of the Commission of Drugs Reimbursement for Inami-Riziv, begun by explaining challenges faced in Europe, and specifically Belgium, for the upcoming EU HTA. The first of these challenges was the upcoming workload and the implementation of suitable methodology in the 15 months left before the launch of the EU HTA. One of the main objectives for the EU HTA is to avoid work duplication and facilitate access, and as the capacity for assessment varies between countries, and the EU HTA is a small part of the process, there is a risk that this additional process will come on top of the assessment process at a national level and increase resource usage rather than streamline and standardise assessment.

Other challenges for Europe with the EU HTA include the necessity for human resources with the correct expertise, the need for real world evidence and its integration, and possibly most importantly, the need for answering the inequalities of access present between countries, which is not considered to be addressed currently by the EU HTA.

Diane went on to state that Belgium has the same challenges and difficulties faced at the European level, but has a head-start in actively fixing this problem. Belgium is currently in the process of implementing a system reform, and this is being seen as an opportunity to integrate the EU HTA in national procedure. Whilst Belgium has this opportunity, other member states will have the challenge of integrating the procedure into already well-established national processes.

Providing a counterpoint to Diane and giving an industry perspective on the EU HTA, Jon Neal, Head of Pipeline and Portfolio for Takeda Europe and Canada, stated that "the devil is in the detail of the process, and the detail is some time away". Comparing the EU HTA to the establishment of HTA in EU member states, John suggested that HTA was an incremental improvement, and a process in which industry was recognised as a partner in its development.

With the EU HTA however, members of the industry are concerned it may be a process where industry input is not considered to as great of an extent. A number of questions will come up through the process, and to successfully launch the scheme, there will need to be widespread collaboration and consultation. John thinks however that currently this is not incorporated in the plan, a fact that needs to change.

The use of PICOs was specifically highlighted as a challenge, as using oncology as an example, the need for over 10 PICOs per indication in an oncology therapy will be tough for the industry to produce and will be even more difficult for orphan diseases.

To conclude the industry perspective, John stated that there are a number of improvements that remain to be made, and to ensure success of the EU HTA, there must be flexibility following launch.

Alexander Natz, Director General of EUCOPE, corroborated John's perspective, and stated that the EU HTA is a positive opportunity and could be the cornerstone for access in Europe if its implementation is done correctly and industry has significant involvement. Alexander's current belief is that the involvement of industry is not being considered to the correct extent, and to keep Europe competitive to other markets, the involvement of both industry and patient organisations will be key.

Fabienne Bartoli, Director General for the French National Authority of Health, provided an interesting comparison of the EU HTA. Fabienne stated that whilst the EU HTA has a number of challenges and unmet needs that must be met, the industry also has to make a big step to be ready to understand the process to utilise the opportunity. Fabienne likened the EU HTA to the launch of the EMA in the 90s and stated that whilst the EMA is a great success and is an integral regulatory body, its build and launch was not without its challenges. The hesitation of countries to accept regulatory decisions and the time taken to buy into the process will be similar for the EU HTA, and John Neal agreed with this point and elaborated that in time, member states will have to change the way they work with a willingness to adopt the new methodology.

Exploring more on the risks and opportunities related to the EU HTA, Tomáš Doležal, Co-Founder of Cogvio, suggested that the EU HTA was a chance to harmonise clinical assessment at the EU level, and an opportunity for countries with limited resources. However, with this opportunity comes the risk for the lack of coordination between EU and national level decision making. Tomáš suggests that proactivity is required, and EU level assessment should be reflected in national HTA, and although these countries will struggle with limited capacity initially, these countries will learn how to implement the EU HTA into the local process to facilitate access.

Jon and Fabienne went on to discuss the clinical assessment aspect of the EU HTA, and Jon stated clinical assessment is half the process and will not encompass value for money and pricing assessment, which is marked as a country level process. As a result, there is a worry that this may add a level of bureaucracy in assessment and increase the risk of work duplication. The overarching impression gained from the panellists is that the EU HTA is a great opportunity for both patients, health systems, and the industry.

The EU HTA would provide in-depth and appropriate clinical information for the use of ODs, and discussion on EU HTA regulation prompts us to talk about the correct methodology for the assessment of ODs and ATMPs. Alexander elaborated that there must be constant interaction, and patient involvement and voice should be treated as integral for the success of the process. Alexander also suggested that we should move away from piloting, as seen with EUnetA and roll out the EU HTA in the hopes it facilitates better, reimbursed access.

The key takeaways

1 SEIZING THE EU HTA OPPORTUNITY FOR ENHANCED ACCESS

The EU HTA, once launched, offers a vital opportunity for improving access in Europe and can be continuously refined for ongoing enhancement.

2 UNLOCKING ACCESS POTENTIAL: THE URGENCY OF EU HTA

Despite the tight 15-month launch window, prioritising patients over industry and incorporating multiple perspectives can facilitate ongoing improvement and reduce bureaucratic hurdles in launching the EU HTA.

3 ADAPTING TO CHANGE

Despite challenges, launching the EU HTA and allowing for ongoing adaptation can lead to successful integration, as seen with EMA regulatory decision-making and evolving HTA systems.

An update on the Nordic HTA Collaboration

During the panel discussion on FINOISE, Maria Eriksson, a medical assessor at TLV, and Ida Kommandantvold, an adviser for HTA hospital medicines in the Norwegian Medicines Agency, shared insights into FINOSE, the joint HTA initiative in the Nordics. Established in 2018 by Finland, Norway, Sweden, and joined by Denmark this year, FINOSE aims to streamline the evaluation process for pharmaceuticals in the Nordics.

We learned that FINOSE still sees itself having a role once the EUHTA is implemented as it will still be responsible for economic evaluations. Additionally, FINOSE saw its benefits as streamlining the access process in the Nordics countries, however, audience members from pharmaceuticals companies shared experiences that were not reflecting this.

The Discussion

The panel provided an overview of the FINOSE process, which involves several key steps.

- First, there is a pre-assessment phase where manufacturers submit a PICO (Population, Intervention, Comparator, and Outcome). This step is needed in order to determine whether the drug is eligible for a joint HTA. If all the health agencies agree on the PICO provided by the manufacturer, the drug is suitable for the joint assessment. Given the similarity in treatment practices across the Nordics, most drugs tend to be eligible.
- Next comes the scoping meeting, where an overview of the process and timelines is provided. This stage allows manufacturers to seek clarification and ask questions about the evidence required for the assessment.
- The manufacturer then submits the HTA dossier to the TLV in Sweden, which is then shared with all other HTA agencies involved.
- Finally a joint report is published which is used to support pricing and reimbursement negotiations at the national level.

The benefits of FINOSE are twofold. For healthcare systems, it ensures equal and timely access to medicines across the Nordics, while also fostering the sharing of knowledge, methodologies, and best practices among HTA agencies. This collaboration helps align methodologies and evidence requirements, reducing duplication of efforts and promoting efficiency. Manufacturers also benefit from FINOSE, as it provides a simplified and efficient way to approach the Nordic markets with a single point of contact.

However, during the discussion, a member of the audience from a pharmaceutical company expressed a negative experience with FINOSE, finding it less compelling than anticipated. They struggled to see the benefits mentioned, particularly in terms of meeting established timelines.

The panellists acknowledged these concerns and admitted that they have faced challenges in delivering within the set timelines. They are actively working to identify the causes of these delays and address them to improve the process.

Participants also raised questions about the future role of FINOSE once the EUHTA (European Health Technology Assessment) is implemented. It was clarified that FINOSE would still be responsible for economic evaluations, even as national HTA agencies adapt to the changes brought about by EUHTA.

The takeaway

While the rationale of aligning evaluation processes is clear, whether this is really translating into faster patient access in the Nordics and into simplified market access for manufacturers is less clear.

Access Opportunities for Rare Disease In and Out of Europe

In this session, representatives from Charles River Associates explore the impact of changing landscapes for access within Europe, and how these changes may impact pharmaceutical launch strategies for future orphan drugs. Developing opportunities and challenges in Europe are contrasted against opportunities in other markets that may be attractive to manufacturers.

The discussion

Charlotte Poon, Senior Associate, and Bhavesh Patel, Principal lead for Charles River Associates, presented gave an in-depth presentation on the rapidly evolving access pathway both inside and outside Europe, and posed the question of whether launch strategies within the current environment should be reconsidered by pharmaceutical manufacturers.

Charlotte described Europe as being in a state of flux, with new pharmaceutical legislation posing the risk of dampening the environment for upcoming rare disease medicines. Charlotte went on to describe this as a "big squeeze" across Europe, driven by the need of cost containment to address affordability challenges. However, what does a good access system look like? Charlotte described a "good" system as being a well-functioning system supporting consistent and stable access to medicines and adhering to 5 general pillars: political prioritisation, R&D incentives, adaptive regulatory pathways, dedicated development of value assessment and flexible pricing and reimbursement models, and a healthcare system that supports efficient diagnosis and treatment of rare disease with quality assurance.

Presenting a positive outlook, Charlotte described several European markets that have made significant progress in becoming a "good" system. Italy introduced tax incentives in 2021, with tax credits of up to 65% supporting the development of research projects for rare diseases. France was mentioned as one of the premier countries to implement a national plan for rare diseases, with it now having a 4th iteration of this plan. Finally, Switzerland was mentioned to be introducing a new process supporting early dialogue to facilitate timely funding decisions from 2024 onwards.

Bhavesh gave a contrasting opinion however, and stated that although there are positives within Europe, the challenges to access in Europe stand out. Recent examples of companies that experienced significant challenges with European launch include Bluebirdbio, who had to exit from the European market even after providing a model for financial payments, and Roctavion, who achieved an ASMR V in France, and a non-quantifiable additional benefit in Germany. Bhavesh gave further examples on orphan drugs that had to withdraw during HTA and pricing negotiations, such as Arikayce who had to stop supply in Germany due to the breakdown of pricing negotiations.

Bhavesh suggested that companies should be looking beyond Europe to other markets, who whilst they have challenges, have growing opportunities for access. Canada for example, a market that is traditionally challenging for orphan drug access, launched its first ever national strategy for rare disease and is now prioritising rare disease and access for patients. The UAE in 2018 developed a fast-track process for orphan drugs and have now committed to the rapid review of orphan drugs. Saudi Arabia have had a revamp to orphan drug guidelines and have developed their attractive breakthrough medicines program.

However, what does this mean for manufacturers? Bhavesh believes that we are now at a cross-roads for opportunities inside and outside of the EU. Increasingly stringent access conditions in Europe will demand: increased agility in launch strategy, the increased robustness of value arguments, the management of expectations, and the increased need for collaborative work across policy makers, payers and the industry in shaping and designing an attractive pharmaceutical ecosystem. Due to the big strides being made by markets outside of Europe in rare disease policies and HTA pathways, Bhavesh suggests manufacturers need to consider how to optimise the willingness to submit to other markets.

A targeting global strategy, earlier launch and the consideration of non-typical launch orders may be beneficial in ensuring successful access for orphan drugs. Bhavesh summarised by stating it is critical to understand how the landscape evolves with rare disease. In the rare disease space, manufacturers must consider which strategy and where the strategy is implemented to elicit the most benefit for their product.

The key takeaways

1

AFFORDABILITY SQUEEZE PROMPTS STRATEGY RETHINK

The European market access environment is in an ongoing state of flux, and is currently subject to a “big squeeze” due to cost containment measures made to address affordability challenges. As a result, pharmaceutical manufacturers may gradually be prompted to reconsider their launch strategies.

2

RISK MITIGATION AND STRATEGIC AGILITY

A number of recent launches in rare disease indications in the EU have failed at the regulatory, pricing and reimbursement, or HTA level. To mitigate growing risk within Europe and maximise the potential success of the product in an evolving environment, manufacturers must implement agility in launch strategy, the increased robustness of value arguments, and the management of expectations.

3

MANUFACTURERS TO OPTIMISE THEIR GLOBAL STRATEGY

Markets outside of Europe are increasingly becoming more attractive to manufacturers, and for manufacturers to obtain optimal access for their product on a global scale, manufacturers should consider willingness to submit to other markets and optimise their global strategy.

Developing Sustainable Models for Access to Rare Disease Medicines in Low and Middle-Income Countries

It is reported that 6.6 billion people live in low and middle-income countries (LMIC), however, drugs for rare diseases often do not reach them.

The discussion

On Day 2 at the World Orphan Drug Congress, we listened to a talk on access to orphan drugs in LMICs. Some access models used in LMICs were discussed:

- The Max Foundation which provides donated medicines from manufacturers and has a network of doctors who can support patients. The Max Foundation is supporting more than 30,000 patients across different LMICs
- The Alagille Syndrome Alliance (ALGSA), a support organization for people affected by Alagille syndrome, procures and distributes medicines to patients
- Guard, which is a more traditional way for access or managed access in these countries for manufacturers in the sense that it works similarly to early access programs across the world but with the understanding commercialization in these countries may be a large challenge

Options are limited and more must continue to be done to improve access in LMICs. Some suggestions from the speaker into methods which could advance the access included:

- Patient and sponsor advocacy pushing for access in a greater number of countries
- Creating physician champions for products in these countries
- Engagement with the Ministry of Health to discuss ways forward for the supply of medicines
- Starting small is okay, smaller initiatives can be then scaled up to help out more and more patients. Just like the Max Foundation which supports thousands of patients.

However, the most interesting opinion, from a manufacturer and market access perspective, was raised by a member of the audience.

In their opinion, it was the IRP that, in many cases, was discouraging pharmaceutical companies from launching in LMIC for fear that launching at an affordable price for LMIC would risk referencing across the world, considerably reducing the price.

Of course, the cost of the drug is only one part of the problem and the limited access to medicines in LMICs, including orphan medicinal products, results from a wide range of causes extending beyond the inability to fund them. The lack of infrastructures allowing patients to be diagnosed and monitored, and products to be stored, distributed and administered is key. However, manufacturers' willingness to launch their products in LMICs at significantly lower prices is a significant step toward expanding access. This willingness may be increased if the repercussions from international reference pricing are removed or reduced.

The takeaway

Manufacturers' reluctance to offer rare disease drugs at lower prices in LMICs due to international reference pricing hinders access expansion. Reducing or removing these pricing barriers can encourage wider availability of medicines in these countries.

Do early access programs always create value?

Early access is a mechanism to allow products to get to patients in need prior to regulatory review or official reimbursement. Typically, only available for drugs for severe diseases, these programs can be life-changing for patients suffering from diseases where there are no suitable treatments. However, by accessing these programs manufacturers must understand and mitigate against the potential risks that surround them.

The discussion

There are several reasons why manufacturers may consider using an early access program which could include getting products to patients sooner, generating early revenue, increasing clinician experience, and collecting additional data.

Beyond considering the feasibility and attractiveness of the program a risk-benefit assessment should also be conducted for each country and each individual program. However, some of the general risks and benefits of a manufacturer considering early access programs (EAPs) are detailed in the table on the following page.

Benefits	Risks
Demonstrates patient centricity	Investment of time and resources from the manufacturer and other stakeholders
Early market access penetration	If treatment or non-treatment-related AEs arise, this will impact regulatory approval
Potential for early revenue generation	If the drug is paid for, the price charged during an EAP is in effect a cap on the final reimbursement price
Gain early launch preparedness	
Opportunity to gain real-world evidence (though primarily on safety)	Uncertainty in demand results in the inability to determine the quantity of drugs to be supplied
Anticipate and set price guidelines for price and access of the drug	Negative public relations and press coverage if the manufacturer is unable to supply the drug or if EAP is withdraw without provision for full access
Strengthen multi stake-holder relationships with regulators, physicians, providers, and patient groups	

Pricing and volume risks can be exemplified by two drugs that were part of the French ATU early access program, Uptravi and Crysvita.

Uptravi – This drug went through the ATU with a much narrower population than their clinical trial (the most severe patients). Higher numbers of patients were dying (many in non-drug related deaths) than in clinical trials, because of the severity of the disease in the patients. This led to a delay in EMA approval whilst a safety investigation was carried out. In turn, this led to a large price reduction in France (36%) and many other markets restricting the population to reflect the French ATU population.

Crysvita – Again this product agreed to a more restricted patient population than their clinical trial for the ATU program in France. Though there was other evidence to demonstrate efficacy in the full population HAS made the decision that it would only give a high SMR rating to the ATU population reducing the reimbursable patient population in France and causing a 25% lower price that that secured as part of the ATU reimbursement system.

Though these two examples displayed an EAP strategy that was not optimal, many products do greatly benefit from entering EAPs. Some factors which could contribute to an EAP success strategy are:

- Ensuring organisational alignment on the reasons to pursue which will allow appropriate pathway selection and country prioritisation.
- Each EU member state has their own decision-making criteria and requirements. So having a European regional policy, which then is tailored to individual market situations is key.
- When making decisions around the design of the EAP programs (e.g. patient caps, price charged, data captured), ensure a downstream view with a thorough risk assessment of impact on final commercialisation outcomes.
- Early engagement with regulators, clinicians, centres and patient associations is imperative for EAP approval and uptake success.

The key takeaways

1. It is imperative for manufacturers to have a clear reason to pursue early access.

2. A thorough review of the downstream consequences for each access program will help to prevent any unwanted negative surprises for the product's launch.

3. Discussions with regulators, clinicians and patient groups must begin early to increase the chances of a successful EAP design.

When the science isn't enough

- **How to navigate policies and gaining market access**
- **Improving access to patients and pushing for sustainability**

Day 3's session on "**when science isn't enough**" provides a number of interesting perspectives of when good clinical data alone has not been sufficient to gain access for those with a need for treatment for rare diseases. The overarching point of the session is that work towards access is ongoing, and in Europe's increasingly challenging landscape, an emphasis is given on supporting clinical data with further activity to allay payer concerns and mitigate challenges for submission.

The discussion

This session consisted of a panel of speakers with a number of different perspectives, including policymaking, patient group, and HTA. Josie Godfrey, from JG Zebra Consulting, moderated the panel and spoke to her experiences at NICE with the highly specialised technology pathway, and stated that although rare diseases are increasingly becoming a focus, the number of rare disease treatments being launched is not enough to meet the unmet need for treatment, even though manufacturers are submitting these treatments to different markets.

Josie discussed how there is often a struggle for funding for research, and once the research is conducted, further struggle to gain access, demonstrating that often, the science solely is not enough. With such a focus on the science and research, Josie suggested that payers and HTA bodies are not engaged with early enough, and this early engagement should be conducted strategically to obtain optimal access.

Josie also discussed the importance of collaboration at different levels in the road to access, and gave a brief description on Project Hercules (Health Research Collaboration United in Leading Evidence Synthesis), a global project bringing pharmaceutical companies together to increase the chances of new treatments for Duchenne muscular dystrophy being made available to patients.

This project brought 13 companies together, involved a number of patient groups, and had significant involvement from NICE to make a change for the access of treatments. To conclude the point, Josie mentioned that collaboration in general whilst essential, does have limits, and even an abundance of evidence will not necessarily ensure uptake.

Fleur Chandler, Head of Market Access for Sanofi UK and Ireland, expanded on the description of the work of Project Hercules, and elaborated that its intention was to truly understand patient quality of life and the patient journey. Fleur, having personal experience with Duchenne Muscular Dystrophy (DMD), related attempting to get access for treatments to rare diseases as a never-ending fight.

Several products have been introduced for DMD, but a limited amount have gotten as far as regulatory approval and access, a fact which is contributed to by the limited patient population in rare diseases. Fleur suggested that with more common diseases, huge patient populations and well-established endpoints makes the process of approval easier. However, with smaller diseases, there are less well-established endpoints, small patient populations, increasing asks from decision makers, resulting in a tiring and difficult journey to approval. The point of Project Hercules, Fleur stated, was to understand not just how endpoints matter to patients, but also what else is important to their patients and families, in the hope that obtaining this information would help build a stronger evidence package.

Fleur concluded her point with stating how expensive undertaking a HTA is for small companies who do not have the resources that big pharma has to conduct everything necessary on top of clinical trials. In Fleur's opinion, cross-body collaboration is essential for access to rare diseases, especially with products from small companies.

Nick Sireau, Chair and CEO of the AKU Society, gave a personal perspective of rare diseases and "when science isn't enough" and mentioned that the support activities must have ongoing commitment and it should not just stop at clinical data submission.

Nick referenced a repurposed drug used for AKU having a negative regulatory decision due to the FDA requiring a single endpoint whilst AKU is multisystemic.

Further down the line, even though funding was raised for clinical trials and EMA approval was gained, HAS in France refused to approve the drug, and analysis of the minutes showed a complete lack of understanding about the drug or trials. Nick concluded that “when science is not enough” a patient group should continue lobbying as there are a number of activities that must be conducted to achieve access for the drug beyond regulatory approval.

Emma Eatwell, Global Practice Director for Global Council, provided an alternative perspective from a policy-making point of view. She agreed with the need for collaboration but thought an integral part of facilitating this is evolution in legislation and policy-making. The new EU pharmaceutical legislation was a welcome review but had specifics that presented challenges, however the principle is that an update is necessary. Emma went on to describe that people can pre-empt the direction of policy makers, exemplifying how in 2016, a mandate was given to the EU commission to review pharmaceutical legislation and look at incentive framework and market access processes. The overarching point was that people should attempt to pre-empt and understand policy changes, and then interact and produce collaborative solutions to existing challenges.

To conclude the panel’s discussion, Chris Grimes Crompton, Senior Associate at Decisive Consulting discussed the practical realities between large and small companies and the development of treatment for innovative diseases in the US and Europe. Chris suggested that a significant amount of innovation in rare diseases comes from the US, and the manufacturers involved often see Europe as a challenge that “will not get any easier”, a sentiment shared by a number of speakers at the WODC. Many US companies launch and Europe and ask “what do we do here” after focusing solely on the science.

Chris suggests that these companies should address uncertainty for those providing primary care, or suffering from the condition directly, and ask these individuals either directly or indirectly to gain a true understanding of what impacts their lives. Chris thinks that whilst not all payer questions will be answered, if this is done early, payer uncertainty can be better addressed, contributing to better access.

The key takeaways

1 CLINICAL DATA IS NOT ALWAYS ENOUGH

Comprehensive clinical data, whilst integral to achieving access for products for rare diseases, may not always be enough ensure optimal access, presenting challenges especially for smaller companies that have reduced resources to support activities beyond clinical trials.

2 COLLABORATION LEADS TO SUCCESS

Cross-body collaboration for Duchenne Muscular Dystrophy has already had some success in attaining access for treatments meeting the unmet need, so continuing collaboration and patient group input is integral to ensuring access challenges can be overcome .

3 GO BEYOND THE DATA AND ADDRESS PAYER CONCERNS

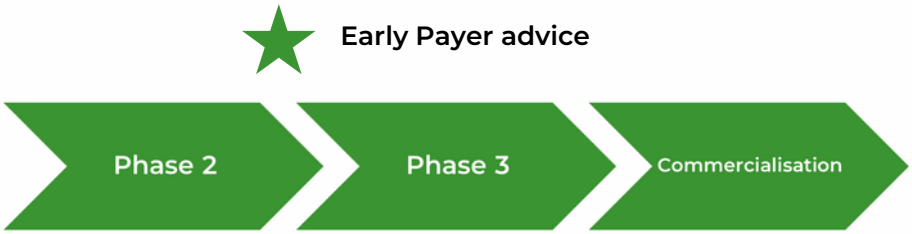
The challenges to access in Europe are becoming a growing point of concern for manufacturers, which begins to impact those needing treatment. Going beyond the submission of data and addressing uncertainty for primary caregivers and those suffering from the disease will contribute to successful access for drugs by allaying payer concerns that are not initially considered.

Rare HTA – Payer advice in rare disease, the formal versus informal advice conundrum

During this session, Initiate's CEO, Andrew Mumford, highlighted the pivotal significance of seeking input and guidance from payers when strategizing a phase 3 clinical trial. He emphasized the value of employing a well-rounded approach, combining both formal and informal methods to garner this essential input.

The discussion

Payer advice plays a critical role in the pharmaceutical development process, particularly when planning a phase 3 trial. Typically, this advice is obtained through the formal avenue of Early Scientific Advice, which occurs between phase 2 and phase 3. Its primary objective is to shape the design of a phase 3 trial in a way that aligns with payer requirements, thereby optimizing pricing and reimbursement outcomes.



An ideal phase 3 trial should:

- Confirm the efficacy of the treatment in a broader patient demographic
- Provide a deeper understanding of the treatment's safety profile
- Assess the long-term clinical benefits of the intervention
- Yield results applicable to patients in real clinical practice

To effectively meet these objectives, it is crucial to obtain payers' advice early in the process. However, the quality of the advice hinges on the precision and relevance of the questions posed, rendering this task one of the most challenging aspects of the process.

In this context, the PICOs framework, (Population, Intervention, Comparator, and Outcomes) serves as a valuable guide for formulating these pivotal questions:

- Population: how should the patient population be defined, considering geographical variations in diagnosis and treatment pathways?
- Intervention: where does the intervention fit within the treatment pathway, especially when the pathway is not well-established?
- Comparator: what constitutes the current standard of care, and what are the most suitable comparators, considering the targeted positioning in treatment pathways?
- Outcomes: which outcomes are best suited for capturing both clinical and economic benefits of the intervention?

Gaining an understanding of payer opinions well in advance is of paramount importance. Early scientific advice yields written recommendations on phase 3 trial design or a plan to address any evidence gaps. It's important to acknowledge that not all issues can be feasibly addressed within the trial, making indirect evidence collection methods invaluable for bridging those gaps and mitigating future challenges.

However, there are several challenges associated with Early Scientific Advice:

- **Limited slots:** not all manufacturers may secure advice when needed, particularly concerning the implementation of the EUHTA from 2025 onward.
- **No guarantee of success**: payer feedback obtained during early scientific advice does not guarantee success at the time of product launch. The advice is non-binding and regulators and payers can alter their perspectives later on. Additionally, it's provided by only a fraction of the payers who will review the dossier, making it incomplete.
- **Unconsolidated feedback:** payers from different countries may offer conflicting perspectives, complicating manufacturers' efforts to prioritize feedback
- **Limited follow-up**: opportunities for follow-up are restricted once feedback is received
- **Implementation hurdles:** manufacturers may find it challenging to grasp how to implement recommendations

Therefore, it is key for the manufacturer to explore additional methods for securing advice. Employing a blend of formal (Early Scientific Advice) and informal methods is recommended to obtain comprehensive and in-depth feedback.

Informal methods for securing payer advice that were mentioned during the presentation include:

- Delphi panels: a structured approach involving multiple payers for formal advice (publishable)
- Advisory board: Collective advice from a group of experts
- Individual payers interviews

The key takeaways

1

DEFINE THE QUESTINS

Identify targeted questions for payers.

2

LEVERAGE MULTIPLE METHODS

Utilise a combination of formal (Early Scientific Advice) and informal methods to gain comprehensive feedback.

3

TAILOR QUESTIONS

Adapt questions to the chosen method.

4

BE PREPARED TO ACT

Readiness to implement advice, whether by adapting trial designs or employing indirect methods to gather essential evidence and address gaps prior to submission.

Early access to help demonstrate the value of Orphan drugs

In this roundtable discussion, panellists discussed real world evidence generation, its use in early access programs, and how the specific design of early access programs and utilisation of data could help demonstrate the value of orphan drugs and enable patient access. Interesting perspectives were provided at a national level from French early access scheme and changes to Belgian pricing and reimbursement, and from a patient level from patient organisations and those receiving treatment.

The Discussion

Opening with an introduction to the different varieties of early access, compassionate use and managed access programs, Rachel Cummings, Principle Consultant at Decisive Consulting, described the importance of early access programs for people with life threatening diseases with no other options. In her presentation, Rachel discussed sources of RWE and how the provision of data on long term safety, comparative effectiveness, and healthcare resource utilisation is key to the successful launch of products in early access schemes.

The overarching theme of this presentation was the importance of RWE, and how RWE data collection was most often used in payer negotiations and HTA submissions for products, with the areas of highest demand for RWE being neurology and oncology. Rachel further discussed that the industry demand for RWE in early access is significant and is showing an annual growing trend in its demand, with 54.2% of NICE technology appraisals between 2010-2020 referencing expanded/early access programs at least once.

Although demand for RWE in early access is increasing, there remains challenges to its utilisation such as the lack of consistent global regulatory guidance.

Concluding the presentation, Rachel stated that although there is a lack of clarity and standardisation between guidelines for RWE collection, there is an ongoing global effort to both improve and harmonise guidance, and there is clear potential for using early access programs to provide data to inform decision making.

Camille Thomasin, Head of the RWE collection unit at Haute Autorité de santé, provided us a perspective from France, a European country with a funded early access scheme. Beginning by introducing the market access pathway in France, Camille discussed how early access gain be gained both prior to, and post-market authorisation, with multiple opportunities in the market access pathway to gain access and provide RWE.

Elaborating on the importance of RWE, especially for orphan drugs with conditional approvals, Camille suggested a number of methods of optimising the use of this data for assessment. This included ensuring early enough access, so the data is available in dossiers for the first assessment, simplification of data points by clinicians, pharmacists, and patients, and the involvement of patient associations. Data quality and exhaustivity, and adapted methodology for the analysis of data were highlighted as key methods of optimisation.

Diane Kleinermans, President of the Commission of Drugs Reimbursement for Inami-Riziv, provided a Belgian perspective, both for ongoing current and future early access and RWE utilisation. Whilst there is an early access pathway in Belgium, Diane suggested that there was no success for pharmaceutical companies undertaking this route due to the cumbersome nature of the procedure. However, Belgium is currently undergoing a huge reform in pricing and reimbursement, which includes the reform of early access to make it more attractive to pharmaceutical companies, and to collect more comprehensive data beyond simply safety data. To facilitate this, Belgium is developing new methodologies for RWE data collection, such as a national platform for the collection and quality assurance of RWE, and the involvement of different stakeholders such as industry, healthcare professionals and patient organisations.

Lucy McKay, CEO of Medics4RareDIseases, provided her own perspective as a family member of an individual who suffered from a rare disease that defined their life.

Lucy stated her belief that RWE is important from a patient perspective due to the marginalisation of individuals within an already marginalised group. The collection of RWE from individuals benefiting from the early access programs would allow people to better understand about the patient group and the reasons that some may miss out on clinical trials.

Lucy went on further to reveal that patients and clinicians rarely understood early access programs in detail and why they should invest time in data collection. To ensure that value could be demonstrated for ODs in early access programs, clinician and patient knowledge must first be increased and the involvement and collaboration of patient groups should be utilised from the beginning. Doing so would be the first step in the journey of demonstrating value within early access programs.

To conclude the discussion on how the value of orphan drugs could be demonstrated in early access programs, Karen Facey, Senior Researcher from the University of Edinburgh, asked what could be done to build better early access programs to gain better RWE data. Karen herself suggested post licensing evidence generation for conditional reimbursement, and that early access programs could be used as a bridge between evidence generation and determining the most important outcomes in routine practice.

Diane stated that physicians and patients should reconsider any reluctance to provide access to data as we live in a system based on solidarity and the data received would have a significant impact, and Rachel suggested that other nations should follow France in how their early access program is maintained and used to generate RWE.

The key takeaways

1

UNLOCKING VALUE THROUGH EARLY ACCESS PATHWAYS

Early access pathways present an ideal opportunity for exhaustive data collection to demonstrate value, and whilst current processes may be cumbersome, countries such as France present a model for the use of early access to generate RWE.

2

THE VITAL ROLE OF PATIENTS

To demonstrate the value of ODs in early access programs, implementing patient involvement and patient/clinician education from the beginning is key, as without this, there is a lack of investment in data collection.

3

NAVIGATING THE RISING DEMAND FOR RWE

The demand for RWE is increasing globally and will grow in its importance in the launch of products. However, the collection of RWE is a challenge due to the improper definition of what specifically must be collected in a particular disease context. To know best how to utilise RWE for orphan drugs, the need for specific data must be defined.

How do HTA agencies use RWE?

How do we try to enhance access and standardise RWE to facilitate rare disease research and access?

Day 2's session on how HTA agencies use RWE presented perspectives from Spain, the UK, and Portugal, as regions with varying levels of RWE utilisation. Representatives from Spain and the UK elaborated on the methodology of the use of RWE and provided examples of successful submissions utilising extensive RWE, and the representative from Portugal highlighted how although challenges to generation exist, RWE was growing in its use in Portugal.

The discussion

In the discussion of how HTA agencies use RWE, we received input from the Spanish and English perspective for established methodology, and input from a Portuguese perspective on how the generation of quality RWE could be developed. Rosa Vivanco Hidalgo, head of HTA for AQuAS Catalunya, initiated the discussion by presenting the decentralised HTA procedure in Spain and how different agencies may generate RWE and work together as a network. Rosa initially presented a number of ways that RWE is utilised by RedETS, the Spanish Network of Health Technology and Services Assessment Agencies of the National Health System. This included the use of administrative databases for epidemiological studies, administrative data from both industry and surveys, screening assessment reports, and the implementation of a new methodological framework for guidelines and clinical decision support tools for rare diseases.

AQuAS, The Agency of Health Quality and Assessment of Catalonia has the goal of generating data and knowledge to improve the quality, safety, and sustainability of the healthcare system in Catalonia, facilitating decision making.

Further describing the use of RWE in Spanish HTA, Rosa summarised how AQuAS have developed guidelines for developing further observational studies with RWE in HTA.

A brief description was given on the conducting of feasibility studies, in which the availability and the source of RWE is analysed, and the use of a study protocol, including templates and checklists that encompass the key methodological points for the generation of RWE: for descriptive purposes, for predictive purposes, for casual inference.

To provide an English perspective of the use of RWE by HTA agencies, Stephen Duffield, Associate Director of RWE methods at the National Institute for Health and Care Excellence, delivered a presentation on the different aspects of RWE use in the UK, how RWE is utilised for managed entry agreements, and provided examples of products with successful launch that implemented real world evidence in their submissions.

Stephen began by discussing the value beyond the QALY, or the quality adjusted life years. QALY is an integral part of HTA assessment in the UK, and demonstrating the dedication of the UK to facilitate access for drugs for rare diseases, NICE considered severity through a QALY of up to 1.7 for a severe disease with an unmet need. Moreover, further considering value beyond QALY, if appropriate the health outcomes of carers is considered in submission. Equity for rare diseases is addressed with the highly specialised treatment pathway, which has specialised committees focusing on rare diseases accepting evidence beyond traditional randomised controlled trial evidence and considering the level of high uncertainty.

Highlighting the importance of RWE, Stephen went on to describe NICE's vision for RWE, highlighting RWE access, the use of RWE, capability building, signposting, and partnership and research being key goals to facilitate the use and further generation of RWE.

NICE's RWE framework, published in June 2022, is a key part of developing this vision, and aims to increase the use of RWE to fill evidence gaps and improve recommendations, improve quality and transparency of RWE studies that inform guidance, inform critical appraisal of RWE studies, and increase trust in high-quality RWE studies. The framework also gives best practices for the planning, conducting, and reporting of RWE.

A key point introduced by Stephen that demonstrates the growing importance of RWE within the UK is the use of managed access agreements.

Stephen briefly the overarching goals of managed access agreements as ensuring patient access whist further data is collected to address key uncertainties identified by NICE, and ensuring the NHS pays a cost-effective price through a commercial access agreement. Recognising that not every drug is suitable for a manged access agreement, the feasibility assessment was introduced, in which questions are asked such as “is the clinical uncertainty for the drug resolvable with data collection”.

New drugs in COVID-19 were presented as examples, with the uncertainty being if there is appropriate data to show treatment will be effective for the next variant after the end of the managed access agreement. In addition to clinical uncertainty, other issues were presented for ongoing data collection, such as issues with data quality, the speed of data collection, and if data collection can start the moment the drug is offered in the NHS as part of the managed access agreement. Stephen concluded his description of barriers to managed access referencing burden on patients and healthcare professionals on the front line, and pressure on the NHS.

To follow the challenges presented, Stephen referenced a case in which the use of RWE was beneficial to the submission of Yescarta, a CAR-T cell therapy, through the Cancer Drugs Fund. RWE was used to contextualise both trial and comparator data using real world studies and demonstrated similar outcomes and baseline characteristics to real populations. RWE was also used to elucidate the expected full cost of treatment, including factors not always considered in pricing such as changes to infrastructure. This benefited and supported the submission of Yescarta, which was associated with longer overall survival than salvage chemotherapy and sustained progression free survival.

To further highlight this point, Stephen presented a number of products that achieved successful access after a managed access agreement utilising RWE evidence, and concluded his presentation with the statement that NICE are dedicated to attaining curative therapies, meeting unmet need for rare disease treatment, and incentivising technological innovation.

To conclude the session and provide a final perspective from a Portuguese point of view. Claudia Furtado, Head of Information and Strategic Planning at Inframed. According to Claudia, unlike in the UK and Spain, Portugal have no real guidance for the use of RWE, but is starting to think about how to generate quality RWE.

Like NICE in England, Portugal grapples with clinical and economic uncertainty due to the lack of comparative data and high rare disease drug costs. Claudia noted the growing utilization of RWE through disease registries to mitigate these uncertainties. However, the challenge remains in integrating RWE into HTA assessments due to concerns about its quality and study design validation in Portugal. Claudia stressed the need for RWE guidance to aid HTA developers and support data generation for advanced therapies and orphan drugs, ultimately benefiting patients.

The key takeaways

1

DECENTRALISATION IN SPAIN

Whilst in Spain, HTA is decentralised, the different manners in which RWE is utilised is combined across the network of HTA to facilitate access for patients in Spain.

2

NICE EMBRACE RWE FOR RARE DISEASES

NICE in the UK continue to demonstrate an increasing willingness to integrate RWE into assessment with extensive RWE methodology to meet the unmet need for rare disease and support the development of innovative therapies for patients who need them most.

3

RWE UTILIASTION IN PORTUGAL GROWS

Whilst no guidance exists for the use of RWE within Portugal, there is a growing utilisation of RWE in forms such as registry data. This suggests a gradual change in perception for the utility of RWE, and RWE as whole has been recognised as essential for patient access to drugs for rare diseases in Portugal.

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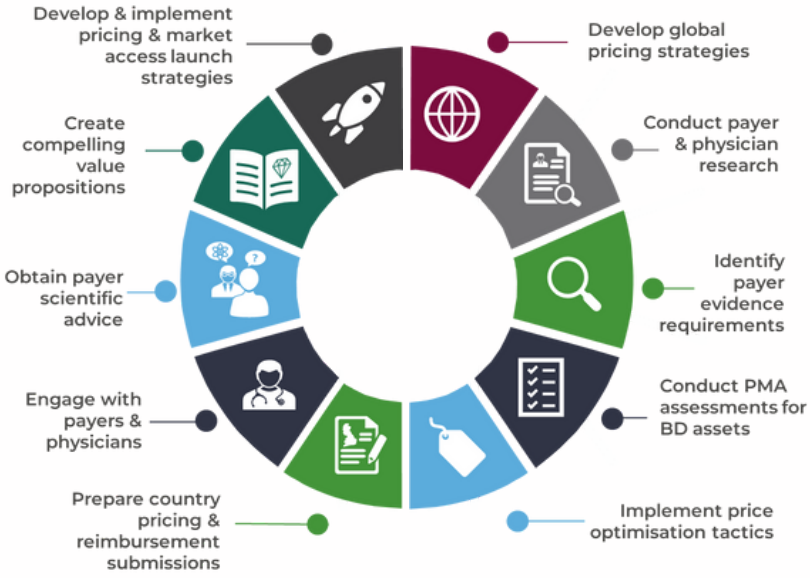

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