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Remap

CONTENTS

ISPOR Europe 2022, Vienna, Austria

Remap Consulting joined over 4,100 other delegates in attending the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting in Vienna, Austria from 6th - 9th November 2022.

The theme for this year's meeting was "Collaborating Across Borders: Building & Using Evidence to Enable Access". The theme was styled as a "thread" that was woven throughout many of the sessions to bring a fresh and holistic view of collaborating across borders for building and using evidence to enable access.

Our report summarises the plenary sessions and our research that we presented at the conference.

Plenary Sessions Overview

The Convergence of HTA and Regulation: A New HTA Reality and Collaboration with Regulatory Agencies

There were two focuses of the panel this first was about the integration of the Joint HTA process and the regulatory process in Europe. Speakers gave their opinions on how these processes could work fluidly together and influence one another. The second topic was the evidence requirements and how to manage satisfying evidence requirements for the regulatory process and the regulation impact.

Convergence of HTA and regulation

The EMA is a long-established regulatory system with a strong network of health agencies. It is helping to provide a strong basis for the formalised EU joint HTA process. The two processes will influence each other, and greater interaction will strengthen both sides. This is because it will provide responses to the patients and connect different areas with different purposes to serve patient needs. A more integrated approach between the two processes will support a greater capacity, foster the best use of resources, and help deliver a common message.

Overall, medical innovation only matters when it reaches the patient. Currently, this is a complex route which much variety in different countries. For the joint EU HTA process to work and to make access more standardised across the EU all of the information will have to be collected to facilitate national decision-making, so as not to delay access. This must be a multi-topic and multi-stakeholder approach to ensure all bases are covered.

Countries in Central and Eastern Europe often suffer from a long access gap following marketing authorisation (for example in Germany access is after an average of 142 days whereas in Poland it typically takes over 500). Several factors are responsible for this, one of which is pharmaceutical company launch sequencing. The joint HTA will really promote the closure of this gap, however, these countries may also be concerned about the financial and budget implications of making a pricing decision will bring. There will also likely be increased pressure to make pricing decisions quickly with the joint HTA process.

Fast-track or conditional assessments from the EMA will have to be carefully considered. They will still have to satisfy all of the information requirements to be approved at the national level, so the JCA process may be a good tool to access the gaps and understand how they can be worked through.

Evidence Generation

Evidence generation must be considered at all times in the product's lifecycle. Though randomised control trials may still be the gold standard it will be important to consider all avenues of information. Post-approval data can be a really valuable tool.

The EU have the DARWIN project in place which is a pan-European network of real-world data. The aim is to help give a greater understanding of diseases, patient populations and the safety of products. This will be especially important for making decisions for products such as gene therapies with small patient populations.

Manufacturers and HTA bodies need to work together early to identify evidence gaps to take the pressure off pricing and reimbursement decisions later. This will allow a greater amount of time for HTA bodies how they can plan to access a product given its evidence gaps.

It will be really key to ensure that there aren't any evidence gaps between the Joint HTA process and then the decisions at the national level as this will slow down access. To overcome this, a structural and strong guideline for evidence generation must be created and it must be considered from all perspectives.

The Key Takeaways

1. "Collaboration is the answer" - The EMA and the Joint European HTA body are in good stead to work together clear convergence between the two will make patient access more fluid
2. "It's the evidence, stupid" - Evidence must be considered across the product lifecycle and the gaps should be considered as early as possible
3. "It's not revolution, it's evolution" - Most HTA bodies have taken over a decade to get to this stage the evolution must continue for this every country needs legislation in place in 2025 so to not delay access

Real-World Patient-Centered Research: Is It Possible Across Countries?

Real World Data is being increasingly used across the globe to support medical-product regulatory decision-making, which fosters the generation and use of Patient Experience Data. This discussion, moderated by Tara Symonds, Clinical Outcomes Assessment (COA) strategic lead & chief science officer at Clinical Outcomes Solutions, explored patient-centred research.

The panellists contributed their own key learnings and insights from current initiatives into capturing patient-centric data and its use in evaluating new medicines to inform future thinking. Topics covered included: the DARWIN (Data Analytics and Real-World Interrogation Network)-EU initiative, examples of Patient Reported Outcomes Measurement (PROMs) programme and their learnings and Core Outcomes Sets (COS).

Harmonisation across borders requires a transparent approach and common understanding

For multi-stakeholder dialogue, a common, robust and meaningful understanding of Patient Experience Data (PED) is required. At a recent European Medicines Agency (EMA) workshop, PED was defined as data collected via a variety of patient engagement activities and methodologies to collect patients' experience of their health status, symptoms, disease course, treatment preferences, quality of life and impact of health care. Patient Reported Outcomes (PROs), Patient Preferences (PPs) and Patient Engagement (PE) are all examples of PED. Common terminology is fundamental to enhancing global discussion.

The workshop also reinforced the relevance of robust methodology to capture and analyse PED to optimise medicines development, regulatory decision-making and HTA assessments. This will require alignment between regulatory and HTA bodies to ensure that data generated at early stages can be used to inform companies' submissions to HTA agencies later.

The DARWIN (Data Analytics and Real-World Interrogation Network)-EU initiative exemplifies the opportunity for digital clinical data generation and analysis.

Institutions working as part of DARWIN have access to healthcare data in a real-world setting.

It is expected that by 2025 the initiative will deliver 150 studies to provide and analyse data to support HTA agencies in their assessment of medical technologies. Arguably, this volume of studies generated provides great clinical data resources however the impact of these studies must be considered, are the outcomes meaningful for the patient?

Reinforcing patient relevance in evidence generation is a key priority for the network. Guidance is critical, beyond that of published documents. Support is required to implement collection of PED, such as establishing a coordination centre. Collaboration centres within Networks is important to harmonise and optimise the data collection process to ensure difficulties are addressed along the way. One example where harmonisation is potentially needed is between national and local levels in countries where discrepancies in data management and safety may exist.

The decisions that the data will inform should be considered when establishing PROMs

Data collection is just the starting point. HTA requires a 'whole-system' approach to evaluate new technologies which considers whether the patient benefit justifies the cost. This requires data on costs and outcomes, giving rise to the establishment of Patient Reported Outcomes Measurement (PROMs) programmes. These are considered as large-scale, routine measurement in real-world settings; implemented as system wide. Many countries have now implemented their own examples of PROM initiatives, UK's private HealthCare Information Network (PHIN), Southern Cross NZ and Sweden's National Patient Quality Registers are just a few examples, to help understand strengthen patient choice, monitor service effectiveness, and improve value for money and evaluate pathways of care, respectively.

Capturing such large quantities of data across borders is only of value if it is clear how the evidence will drive healthcare improvements for patients. Careful stakeholder engagement is required to inform the decision of instrument choice and to provide analyses that are 'fit for purpose' and meaningful to patients.

Methodological challenges should also be considered, such as case-mix adjustment is crucial to the credibility and validity of the data. For instance, if between-provider comparisons are a goal, appropriate case-mix adjustment is essential. Also, we need to think beyond feasibility in data collection. We know it is possible to collect data at scale, but we need to ensure good response rates. Approaches can include both incentives that could arguably promote a more genuine belief in the data, but lower responses versus mandatory regulations which are not always so well received but could lead to higher response rates. Finally, to capture the essence behind patient-centred research, the evidence must be provided in a way that is meaningful to patients. Dissemination of information must be addressed appropriately.

Standardising patient-centred research can relieve burden but must not lose relevance

Patient-centred research must be informed by patients to be important and meaningful. So, what is meaningful to patients? In the US, the development of a framework has begun (Figure 1) and has been run in pilots. The patient-centred core impact set (PC-CIS) is a patient-derived and prioritised list of impacts on a patient's health and daily life and that of their family and caregivers. It incorporates this with information from other stakeholders, which is combined through a 'prioritisation process'. However, the process ensures the patient voice remains intact and is not outvoted with the other information.

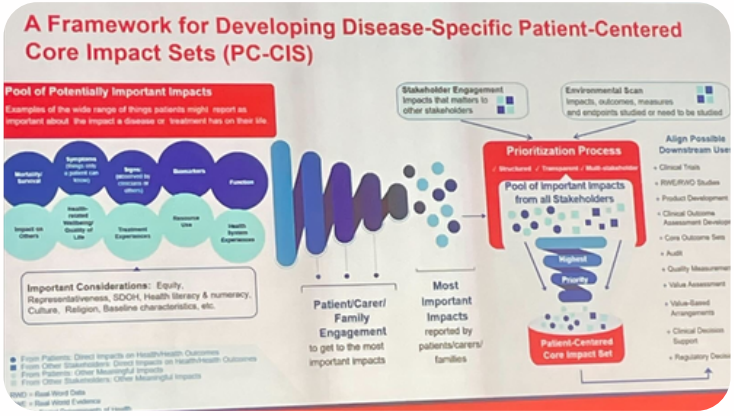

FIGURE 1

Implementing a framework such as the PC-CIS could help streamline data collection, preventing the need for it to be collected repeatedly. In pursuit of efficiency, we must ensure that relevance is not lost, and that the tool is able to effectively answer the situation-specific question being asked and inform relevant decisions.

A Core Outcome Set (COS) is an agreed-upon, standard list of outcomes that should be measured and reported, as a minimum in all clinical trials. A method to assist with ensuring the COS is patient-centred and can contribute to meaningful change is the impact to endpoint pathway.

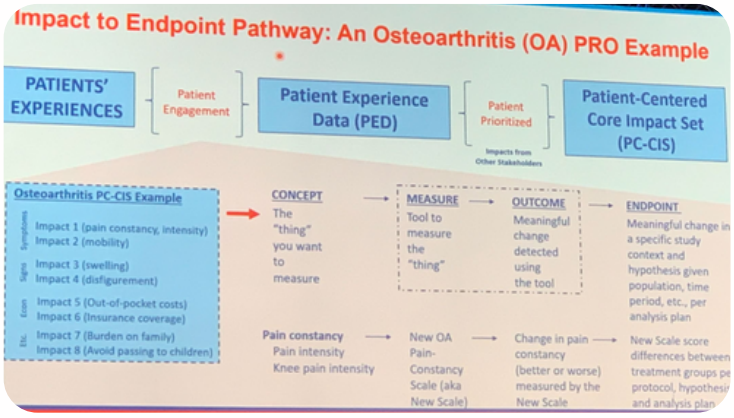

FIGURE 2

Figure 2 demonstrates this using an Osteoarthritis (OA) PRO Example. These frameworks are recommended as 'blueprints' to allow for adaptation to other diseases, or made country or region specific, as examples.

In the US, it is envisioned that access to such blueprints can be facilitated through patient communities sharing to their own website to make publicly available. The idea of a central depositary is also being explored which perhaps could be more viable to assess the potential of these frameworks in Europe. The bottom-line vision is that such frameworks should be publicly available, to empower patients and utilise data to improve and reinforce relevant change.

The Key Takeaways

1. **Patient-centered versus patient-informed** - Data collected about patients must be meaningful to inform decisions that will have benefits for the patient
2. **It's all in the endgame…if you get it right at the start** - Time should be taken at the start to understand what is important for the patient, this will guide the correct data to be captured ensuring the potential for vast amounts of data to be collected has a purpose
3. **We learn from experience** - Current PROMs should be evaluated to ensure they are being implemented in a way that benefits the patient. Ongoing maintenance will be required to inform instruments to make data country or region specific

Innovative Methods for Integrating Data Across Outcomes and Borders

The final plenary session was a discussion on innovative methods for integrating data across outcomes and boarders. The discussions were focused on how real-world data can be used for decision making at both a regulatory and HTA level and how we can optimise the methods for data collection to make it most beneficial across the board. This is of increasing importance as the amount of real-world data continues to expand in volume, granularity, and heterogeneity.

Though it was stressed that randomised control trials remain the gold standard of evidence for understanding the safety and efficacy of any new product, the panel discussed the ideal methods to expand the evidence base for a product via real world evidence. This type of data can be valuable when randomised control trials cannot be performed, they do not cover a sufficiently long-time horizon or if they have used surrogate endpoints. However, for this evidence to be valuable and usable for decision makers there must be processes for integrating data from numerous countries and sources as well as implementing views of what makes good evidence from multiple stakeholders.

We heard about this issue from a regulatory viewpoint, by Peter Arlett of the EMA, where it was the opinion that a research question should be used to guide the evidence requirements but that we must embrace the whole spectrum of evidence methods. For real world evidence there should be a high level of transparency so that trust can be built to enable good data sharing platforms and that the patient voice must be used to guide the types of data being collected.

The DARWIN EU programme was brought up again in this plenary session (see our overview of ISPOR plenary session 2 for further information), as a means to proficiently collect real world data in a way that can be scaled up to be analysed across countries to support in decision making at both the regulatory and the HTA level.

From Shahid Hanif of the GetReal Institute we heard about the European Health Data Scape that is being developed to get health data to be more effectively used across Europe.

It aims to do this by using both primary data, where patients have access to their own data in different countries if the move or are just visiting, and secondary data which aims to facilitate innovation and enable better policy making. With secondary data the aim is to have a catalogue of different data sources brought together that could be used to support decision making by helping with epidemiology assessments, looking at predictions and regional effects and linking treatments to outcomes. The European Health Data Scape is calling for strong involvement into it's development from a wide range of stakeholders- including a need for citizen and patient representation to build trust.

The final talk was from Beate Jahn from UMIT who explained the public health trade-offs between incremental benefits costs in health economics. Using the models shown to the audience, the importance of having as much data as possible to build the comprehensive incremental cost harm ratio was explained as it gave out the best predictions of effectiveness. This type of model differs from an aggregated framework, such as when calculating QALYs, as they are disaggregated and can capture a higher granularity (including things such as short-term effects like anxiety over treatment) and therefore better inform decision making. Many of the trade-offs incorporated into these models would typically not be collected in a randomised control trial.

The Key Takeaways

1. A plethora of data must be used to inform on both regulatory and HTA decision making including both randomised control trials and real-world evidence
2. Collaboration and commitment are required to from multiple stake holders to ensure that evidence is collected in a way that it can be valuable across many causes
3. When data is collected the research question must be considered so that the relevant benefits and trade-offs can be collected for the stake holders

Remap Consulting Research Posters

We're pleased to have presented six pieces of research at the conference, with one poster being awarded a top 5% commendation.

If you would like any further information on the plenaries or research presented below, please contact Paul or Graham at contact@remapconsulting.com

HTA58

Does NICE'S STA Process Effectively Reward the Value of Double-Branded Oncology Combinations, When Compared to Oncology Monotherapies?

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Introduction and Objective

- The role of combination therapies in oncology is growing, with combination therapies becoming the standard of care in many cancers.
- The scientific rationale for this is clear: targeting a key pathway at multiple points, or targeting multiple key pathways, can have an additive or synergistic effect on the efficacy of anti-cancer therapy.[1]
- However, it is unclear whether existing Health Technology Assessment (HTA) processes, designed for the appraisal of single products, can adequately reward the value of combination therapies.
- This research in particular focuses on the Single Technology Appraisal (STA) process conducted by the National Institute for Health and Care Excellence (NICE).
- The aim of this study is to compare outcomes for monotherapies and combination therapies, looking at success rate, number of terminated appraisals, Cancer Drugs Fund (CDF) utilisation, financial agreements, and time from final scope to publication of Final Appraisal Document (FAD).

Methods

Figure 1: Methodology used in this research:

*STAs that were abbreviated or re-assessments were excluded for analysis.

- Pre-determined parameters are defined in the Introduction.
- Table 1 defines the different combinations used in this research.

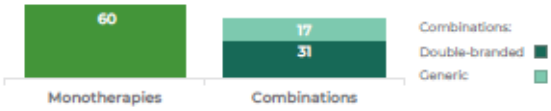
Table 1: Combination definitions

Double branded combination	Generic combination
Combinations comprising of two branded products at the time of launch	Combinations comprising of a branded product at the time of launch with a generic backbone (including chemotherapy)

Results

- 108 oncology STAs published in the study period met the criteria (i.e., not abbreviated appraisals or re-assessments) and were included in the analysis.
- Figure 2 illustrates the breakdown of therapies included in analysis.

Figure 2: Monotherapies and combinations within the study period

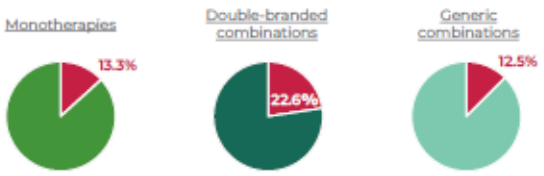


- Success rate was analysed, defined as the proportion of appraisals that resulted in a 'recommended' or 'optimised' outcome.
- As shown in Figure 3, success rate was similar for monotherapies and generic combinations, but lower for double-branded combinations.

Figure 3: Comparative success rates for the STAs of monotherapies, double-branded combinations and generic combinations in oncology

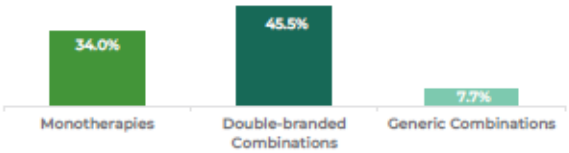
- Since NICE's 2018 decision to evaluate all new chemical entities and significant new indications, terminated appraisals have become more common, occurring when companies choose not to submit following an invitation from NICE.
- This analysis found that while monotherapies and generic combinations had a similar rate of terminated appraisals, the rate was notably higher for double-branded combinations, as outlined in Figure 4.

Figure 4: Comparative rate of terminated appraisals for monotherapies, double-branded combinations and generic combinations in oncology



- Financial agreements were used across almost all oncology appraisals, for 97.7% of monotherapies (all but one) and 100% of all combinations.
- However, there is more variation in CDF utilisation rate. As illustrated in Figure 5, double-branded combinations were more likely to use the CDF than monotherapies; the rate for generic combinations was surprisingly low.

Figure 5: Comparative rates of CDF utilisation for monotherapies, double-branded combinations and generic combinations in oncology



- Figure 6 shows the time from final scope to FAD publication, which was similar between monotherapies and double-branded combinations, although longer for generic combinations.

Figure 6: Time from final scope to FAD publication

Discussion and Conclusion

- Double-branded combinations have the lowest success rate, and manufacturers are almost twice as likely not to submit these therapies to NICE.
- Both of these figures suggest it is more difficult to prove the cost-effectiveness of double-branded therapies under the current STA process.
- When submitted and recommended, double-branded therapies are the most likely to utilise the CDF, suggesting these have the highest levels of uncertainty.
- Overall, this leads to proportionally fewer double-branded therapies getting access, and proportionally higher getting only temporary access (CDF).
- Where data for generic combinations is notably very different from the other two categories, we believe this may be due to the small sample size (N=17).
- However, where there does not seem to be anomalous data, the outcomes for generic combinations most closely resemble those of monotherapies'.
- The similarity between key outcomes for generic combinations and monotherapies may support the idea, proposed by Briggs et al, that it is the branded backbone consuming payer willingness-to-pay thresholds, making it difficult for double-branded combinations to demonstrate cost-effectiveness.[2]
- Overall, this initial analysis suggests that the NICE STA process may not adequately reward the value of double-branded combinations, leaving patients unable to access some potentially life-saving treatments.

CDF: Cancer Drugs Fund; FAD: Final Appraisal Document; HTA: Health Technology Assessment; NICE: National Institute for Health and Care Excellence; STA: Single Technology Appraisal

References: 1 Mokhtari RB, et al. Combination Therapy in Combating Cancer. Oncotarget. 2017;8(23):38022-38043; 2. Briggs AH, et al. White Paper: An Attribution of Value Framework for Combination Therapies, 2021. Available at: https://www.takeda.com/en-gb/what-we-do/combination-treatments/ [Accessed 2nd Sep 2022]

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HPR138

Comparing and Contrasting Early Access Opportunities Across the EU4 and UK

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Introduction/Objective

- Early access programs (EAPs) help to give people with life-threatening or seriously debilitating conditions early access to new medicines that do not yet have marketing authorisation. They have clear benefits for patients, healthcare providers, payers and pharmaceutical companies. Manufacturers, for example, can benefit from generating real-world evidence which can facilitate their pricing and reimbursement (P&R) negotiations with payers, and patients can access critical medicines that are not yet commercially available.
- This study aimed to assess the opportunity for manufacturers to access EAPs across the EU4 and the United Kingdom (UK).

Methods

- EAPs available as of July 2022, in the EU4 and UK were identified through secondary research; extraordinary single patient requests were excluded as deemed not commercial opportunities.
- Eligibility criteria, resource requirements, evidence generation possibilities and timelines were extracted for each EAP. (Figure 1)
- The relative opportunity value of each EAP, for manufacturers, was evaluated.

Figure 1: Methods flow diagram

Results

- A total of seven early access programs were identified across EU4 and UK. Of these, France and Italy all had two program options and the UK, Germany and Spain had one.
- Fundamental to all schemes was the condition that the therapy is to treat a life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorised medicine1 although demonstration of innovation was not a criterion for all.
- Eligibility for the UK EAMs scheme was dependent on obtaining PIM designation and positive EAMS scientific opinion. PIM designation will be issued after MHRA scientific meeting and could be given several years before the product is licensed.
- Most countries did not have a requirement for the company to have marketing authorisation for the product. However, in Germany and Spain an application must have been submitted. In France, the manufacturer has the option to apply to the Early Access Authorisation either pre- or post-marketing authorisation.
- Given that a condition of EAPs is typically the rarity of the disease, expectations for clinical data packages were variable. The UK required evidence from phase III trial unlike Italy that accepted phase I (compassionate use) or II (Law 648) trial data
- In addition to clinical data requirements, France's AAP required inclusion of protocol therapeutic use (PTU) and Italy's law 648/1996 requires a scientific report outlining proposed therapeutic plan, estimated patients and cost for submission.
- Both France's Early access authorisation (AAP) and UK's Early Access Medicines Scheme (EAMS) provided data collection opportunities that could be utilised in their respective HTA bodies' assessment procedures. Other countries considered the data collection opportunities insufficient in the program compared to clinical trials.
- Only France's AAP and Italy's 648 program offered paid Early Access for manufacturers.

Table 1: Framework

Program	Demonstration of innovation	MA Requirements	Clinical data requirements	Eligibility criteria	Evidence generation	Funding opportunity
Early Access Authorisation (AAP)		Post and pre-MA options • Manufacturer must agree to apply for MA once EA granted and submit a request for reimbursement within one month of being granted MA	Protocol therapeutic use (PTU)	1. Presumed efficacy + safety 2. Serious, rare or disabling disorder 3. No appropriate therapy 4. Initiation cannot be delayed	Data can contribute to TC assessments	Free pricing but subject to a double system of rebates
Compassionate use access (CUA)				1. No commercialisation plan 2. No treatment alternative 3. Presumed efficacy + safety		If the product is not reimbursed in another indication, then free pricing
Arzneimittel-Härtefall-Verordnung (AMHV)		Application for marketing authorisation has been submitted or a clinical trial is being conducted on it.		Patients must have a disease that leads to severe disability or is life-threatening and unsatisfactorily treated with approved drugs	Cannot be used	Manufacturer provides free of charge
Law 648/1996			• Phase II trial • A scientific report;	1. No valid therapeutic alternative available 2. Acceptable risk profile 3. Efficacy demonstrated		• Price set by manufacturer if not yet reimbursed in other indications (reimbursement price if available) • Reimbursed by National Health Service
Compassionate Use		Medicines may not yet be authorised but must be involved in a clinical trial; medicines may have MA in other indications; or authorised but not available in national territory	Phase I sufficient for rare disease	1. For use outside the indication of the clinical trial, or where the patient cannot be included 2. Favourable opinion from the Ethics Committee which clinical centre submitting request belongs		Supplied free of charge by the manufacturer
Early Access to Medicines Scheme (EAMS)		PIM designation issued post-MHRA scientific meeting and could be given several years before the product is licensed	Phase II trial (phase II may be accepted in exceptional circumstances)	1. PIM designation: High unmet need; Serious or life-threatening condition; Therapeutic advantage; Positive risk: benefit ratio 2. EAM Scientific opinion	Use in HTA generated during EAMS period in NICE appraisals	Company provides free of charge during the EAMS period and up until the point of a positive funding policy
The Royal Decree 1015/2009 (Authorisation for Temporary Use)		Company must have applied for MA, or be at a stage of clinical research designed to support an MA		1. No therapeutic alternatives 2. Serious disease 3. Patients not eligible for clinical trials 4. Intended to be used for significant group of patients		Reimbursed on case-by-base basis

Required | Not specified | Not required

Discussion and Conclusion

- Through undertaking this analysis, we have been able to populate a framework for early access opportunities, showing variation in qualifying criteria and evidence collection possibilities.
- There are multiple opportunities for EAPs for manufacturers across the EU4 and the UK, although only France and Italy provided paid access that allow manufacturers to set a price for their product.
- The limited number of EAPs that offer paid access could significantly limit the number of manufacturers able to provide early access to potentially life-saving medicines for patients. However, manufacturers need to weigh up the cost of providing their products against the valuable opportunity for engagement with stakeholders and collection of additional data that could be involved in future provision, reimbursement and funding.

AAP: Early Access Authorisation; EAMs: Early Access to Medicines; EAPs: Early Access Programs; HTA: Health Technology Assessment; MHRA: Medicines and Healthcare products Regulatory Agency; PIMS: Promising Innovative Medicine; PTU: Protocol for Therapeutic Use

References: 1. Early Access to Medicines. Development support and regulatory tools. Available at: https://www.ema.europa.eu/en/documents/leaflet/early-access-medicines-development-support-regulatory-tools_en.pdf [Accessed 28/09/22]

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HPR183

Could Netflix Based Subscription Models Tackle the Shrinking Antibiotics Pipeline?

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Introduction/Objective

- After a boom of antibiotic discovery between the mid-1940s and 1980, the discovery of new antibiotics has been largely void in the last 40 years.1
- Concerns have been growing over the limited number of antibiotics in the clinical pipeline as antibiotic resistance is an ever-increasing issue.2
- One barrier to discovery is the poor revenue that antibiotics bring to manufacturers, as price and volume potential is low and new antibiotics are typically only used after earlier lines have proved ineffective. Governments around the world are looking to incentivise novel antibiotic discovery.
- One way in which this is being trialled is with subscription-based or "Netflix" style pricing models. Such models allow manufacturers to be reimbursed for a fixed "subscription" fee irrespective of the volume of the drug that is used for a fixed time period.
- To understand how subscription-based models could address the growing concern of a shrinking antibiotic pipeline, we identified agreements of this type for antibiotics in Europe, along with other therapy areas in the rest of the world, and assessed whether their implementation has coincided with an increase in antibiotic clinical development.

Methods

- Antibiotics and antibacterials assessed by the European Medicines Agency (EMA) since its formation in 1995 were filtered, removing withdrawn or generic applications, and submissions per year were counted.
- Subsequently, European antibiotic subscription-based models were identified from national reimbursement agencies.
- Finally, pipeline antibiotics and antibacterials were visualised over time by analysing World Health Organisation (WHO) data on substances in pre-clinical development since 2019 and clinical development since 2017, which is when records began.

Results

- Since 1995, 21 new antibiotics or antibacterials have been approved by the EMA (Figure 1).
- There was a peak in approval of antibacterials and antibiotics in 2015 following the discovery of a new class of antibiotics (Figure 1).[3]

Figure 1: Number of antibiotics and antibacterials approved by the EMA per year since 1995[3]

- Two European countries were identified which have used subscription-based models to incentivise antibiotic and antibacterial development (Table 1).
- The UK announced in 2022 that two antibiotics will enter this type of model and Sweden has been trialling this model for five antibiotics since 2018.[4,5]

Table 1: Subscription-based models identified for antibiotics in Europe[4,5]

Country	Product	Manufacturer	Year Initiated
UK	Avycaz	Pfizer	2022
UK	Fetroja	Shinogi	2022
Sweden	Zerbaxa	MSD	2018
Sweden	Recarbrio	MSD	2018
Sweden	Fetcroja	Shinogi	2018
Sweden	Vaborem	Pharmaprim	2018
Sweden	Fosdomycin infectopharm	Unimedic Parma	2018

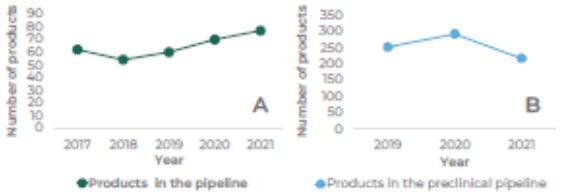
- Outside of Europe, Netflix-style pricing models were identified in Australia and via Medicaid in the states of Washington and Louisiana in the US, all for the treatment of hepatitis C (Table 2).[6,7]

Table 2: Subscription-based models identified worldwide excluding Europe for hepatitis C[6,7]

Country	Product	Manufacturer	Year Initiated
US	Mavyret	AbbVie	2019
US	Epclusa	Gilead	2019
Australia	Sovaldi	Gilead	2015
Australia	Epclusa	Gilead	2017
Australia	Harvoni	Gilead	2016
Australia	Viekirax Pak	AbbVie	2017
Australia	Zepatier	Mereck	2017
Australia	Daklinza	BMS	2017
Australia	Viekirax Pak + ribavirin	AbbVie	2017

- WHO data show an upward trend in antibiotic and antibacterial products in the clinical development pipeline since 2017 (Figure 2A).[8]
- Data from the preclinical development pipeline were available from 2019, but do not show an increase in number (Figure 2B).[8]

Figure 2: Number of antibiotics and antibacterials products in the clinical (A) or preclinical (B) development pipeline[8]



Discussion and Conclusion

- Antibiotic resistance is a global concern which has sparked some governments to incentivise antibiotic/antibacterial research and development. Though subscription-based models for antibiotics/antibacterials correlate with an increase in the number in clinical development, it is unclear if this will translate into more antibiotics coming to market, whether the increase will be sustained, or is indeed if it is as a result of the recent incentives.
- Nevertheless, guaranteed revenue following successful negotiation is likely favourable to manufacturers when development in this area had previously been non-viable. However, both manufacturers and payers may be cautious of these agreements. If epidemiological data are underestimated, manufacturers could receive a very low price per unit. For payers, if long-term health benefits are not realised, they may be tied into a long-term contract.
- Subscription-based models are also used for hepatitis C in Australia and is some US states via Medicaid to allow greater coverage for expensive treatments, which differs from the motives seen for antibiotics. We speculate that subscription-based models may expand into therapy areas with uncertainty over patient numbers or frequency of treatment. However, they may only be feasible in single-payer markets in therapy areas perceived as national future health threats.
- Other innovative incentives are also being proposed for antibiotics in Europe, namely a voucher scheme named the "Transferable Exclusivity Extension" which would provide extended exclusivity to a drug of the manufacturers choice following the approval of an antibiotic.[9]

Abbreviations: BMS: Bristol-Myers Squibb; EMA: European Medicines Agency; MSD: Merck Sharp & Dohme; R&D: Research and Development; WHO: World Health Organisation

References: 1 - Silver LL. Clin Microbiol Rev. 2011 Jan;24(1):71-109; 2 -Butler MS et al. Antimicrob Agents Chemother. 2022 Mar 16;66(3):e0199; 3- EMA. European public assessment reports. shorturl.at/jrTU89. Accessed 23rd Sept 2022; 4 – gov.uk. Development of new antibiotics encouraged with new pharmaceutical payment system. shorturl.at/ajlq4. Accessed 23rd Sept 2022; 5 – Folkhalsomyndigheten. Availability of antibiotics. shorturl.at/CDGJI. Accessed 23rd Sept 2022; 6 - Moon S et al N Engl J Med. 2019;380(7):607-610; 7 – Harry H et al. RAND Corp. 2020; 8 – WHO; Antibacterial agents in clinical and preclinical development: an overview and analysis; shorturl.at/fmST3. Accessed 23rd September 2022; 9- EFPIA. shorturl.at/cjanQ. Accessed 10th October 2022.

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HPR175

Is International Reference Pricing Applied Consistently at Pharmaceutical Price Re-evaluation for Retail and Speciality Products?

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Introduction/Objective

- International reference pricing (IRP) is a price control mechanism whereby medicine prices are calculated based on their prices in other markets to ensure the country determines an appropriate price.
- IRP is used extensively to determine the launch price of new pharmaceuticals in Europe and some countries use IRP during product re-evaluations. In some cases, IRP is used formally, with strictly defined referent baskets and re-evaluation frequencies, whereas other countries use it informally just to inform and sense-check medicine prices.
- The aim of this research is to determine how consistently IRP is applied in pharmaceutical price re-evaluation in Romania, Switzerland, Slovenia and Turkey and assess if IRP is applied stringently for retail and speciality products across these markets.

Methods

- To be included in the analysis, countries had to use IRP at pharmaceutical price re-evaluation, have had stable IRP rules over the past five years and refer to no more than 12 countries. Thus, four countries were identified - Romania, Switzerland, Slovenia and Turkey. Their IRP rules and country baskets are presented in Table 1.

Table 1: IRP rules, country baskets and frequency of re-evaluations of the countries in scope

Country	Flag	IRP rule	IRP basket	Frequency of re-evaluation
Romania		Average of three lowest ex-factory prices	Austria, Belgium, Bulgaria, Czech Republic, Germany, Greece, Hungary, Italy, Lithuania, Poland, Slovakia, Spain	60 months
Switzerland		Average ex-factory price	Austria, Belgium, Denmark, Finland, France, Germany, Netherlands, Sweden, UK	36 months
Slovenia		Lowest ex-factory price	Austria, France, Germany	6 months
Turkey		Lowest ex-factory price	France, Greece, Italy, Portugal, Spain	12 months

- Five retail products (Jardiance, Brintellix, Relvar Ellipta, Enstilar, Entresto) and five specialty products (Eylea, Ofev, Uptravi, Lymparza, Actilyse) which cover a variety of therapeutic areas were initially analysed. Historic price data on the most widely sold pack sizes of these products was provided by Boehringer Ingelheim and IRP rules from 2017-2022 were extracted from public records. One product, Enstilar, was excluded from the analysis as it has not been launched in the countries in scope.
- Analysis was conducted to compare the IRP price against the published price at an ex-factory level to assess how strictly IRP was applied over the years, and if it was applied consistently for retail and specialty products. The drug IRP prices were calculated taking into account IRP rules for all countries each year. Mean annual currency exchange rates were applied, where necessary, to convert local currencies to Euro.

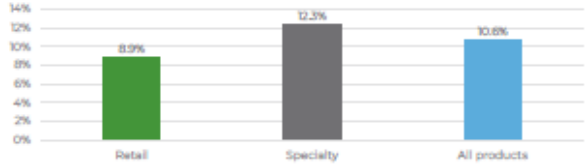
Results

Table 2: Difference in ex-factory price and IRP price across 9 products

Type	Product	Real price	IRP price	Difference	Real price	IRP price	Difference	Real price	IRP price	Difference	Real price	IRP price	Difference
Retail products	Jardiance	€31.65	€28.27	11.9%	€43.20	€38.69	11.7%	€33.00	€33.00	0.0%	€33.00	€33.00	0.0%
	Brintellix	€19.44	€22.38	-13.1%	€36.32	€29.09	24.9%	€20.20	€20.20	0.0%	€20.20	€20.20	0.0%
	Relvar Ellipta	€30.43	€25.32	20.2%	€38.15	€28.11	35.7%	€35.52	€25.13	41.3%	€24.76	€25.13	-1.5%
	Entresto	€100.67	€110.83	-9.2%	€120.26	€119.05	1.0%	€115.41	€104.98	9.9%	NA	€104.98	NA
Speciality products	Eylea	€540.70	€615.79	-12.2%	€886.68	€775.25	14.4%	NA	€565.00	NA	€565.00	€565.00	0.0%
	Ofev	€1,866.39	€1,893.37	-1.4%	€2,540.76	€2,207.22	15.1%	€2,060.41	€1,978.80	4.1%	€1,996.72	€1,978.80	0.9%
	Uptravi	€2,512.07	€3,873.93	-35.2%	€4,317.86	€3,238.53	33.3%	€2,115.00	€2,115.00	0.0%	€2,973.21	€2,115.00	40.6%
	Lymparza	€2,051.75	€2,547.42	-19.5%	NA	2,376.46	NA	€2,529.64	€2,387.93	5.9%	NA	€2,387.93	NA
	Actilyse	€311.55	€306.08	1.8%	NA	512.91	NA	€574.96	€332.40	73.0%	€583.23	€332.40	75.5%

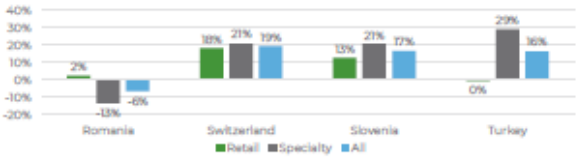
- The individual results from the analysis for each drug are presented in Table 2, which shows data on their real price, IRP price and % difference between the two.
- Across all products and countries in scope, public ex-factory prices in the period 2017-2022 were 10.6% higher than IRP prices.
- The difference for specialty products (12.3%) was higher than retail products (8.9%) across all markets (Figure 1).

Figure 1: Average difference between ex-factory prices and IRP prices across all products in all countries in scope



- Romania was associated with the lowest price difference, where ex-factory prices were on average 6.3% lower than IRP prices (Figure 2). In Turkey, Slovenia and Switzerland public ex-factory prices were 16.5%, 16.8% and 19.4% higher than IRP prices for all products, respectively.
- Retail product ex-factory prices in Turkey and Romania were consistent with the IRP prices, with differences of -0.5% and +2.5%, respectively.

Figure 2: Average difference between ex-factory prices and IRP prices across all products by countries



Discussion and Conclusion

- The results from the analysis indicate that Romania applies IRP at its price re-evaluations processes more consistently than Switzerland, Slovenia and Turkey.
- Also based on the outputs of this research, there is a greater difference between the IRP price and ex-factory price of specialty medicines than retail products across all countries in scope. This could be explained by the generally higher prices of specialty drugs than retail products, hence a wider price differential.
- Ex-factory prices tended to be higher than the IRP prices, particularly in Switzerland and Slovenia, which suggests that factors other than IRP contributed to price setting in these countries.
- It would be interesting to continue to monitor these prices to see if IRP is applied more stringently at national price re-evaluations.

Abbreviations: IRP: International reference pricing

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HTA67

DO MANUFACTURERS STILL SEE A VALUE IN SUBMITTING EVIDENCE FOR A NICE APPRAISAL IN ENGLAND?

COMPARING AND CONTRASTING TERMINATED APPRAISALS BETWEEN ONCOLOGY AND NON-ONCOLOGY AND MONOTHERAPIES AND COMBINATION PRODUCTS

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Introduction/Objective

- Since 2018 NICE has stated it will evaluate all new active ingredients and major new indications.[1] Significantly increasing the number of evaluations conducted by NICE. Additionally, in 2018 they introduced a fee for these assessments. The fee was £126,000 when first charged in 2019, and now stands at £142,800.[2]
- A positive NICE assessment is key to obtaining reimbursement on the NHS in England and Wales. If manufacturers fail to submit an evidence package to NICE, it results in a "terminated appraisal", actively foregoing access to the market.
- This research aimed at identifying trends in terminated appraisals in relation to therapeutic area, monotherapy vs combination regimen, and date of termination.

Methods

- This study reviewed Single Technology Appraisals (STAs) and Highly Specialised Technologies (HSTs) published on the NICE website between January 2017 to May 2022.
- Appraisals listed as "Terminated appraisal – non-submission" were identified and data were extracted on disease area, active substance, (monotherapy vs combination drug), and date of termination.
- A comparison of the number of terminated appraisals between non-oncology and oncology products and between monotherapies and combination drugs was made.

Results

- A total of 358 NICE STAs and HSTs between January 2017 and May 2022 were identified and included in the analysis.
- Of these, 60 (17%) were terminated appraisals due to non-submission (Figure 1).
- All terminated appraisals were STAs.
- Figure 2 breaks down the percentage of terminated appraisals per year. The annual percentage of non-submissions was generally between 15% to 22%, except in 2018 where only 4% of appraisals were terminated.

Figure 1: Proportion of all STAs and HSTs that were terminated appraisals from 2017 to 2022

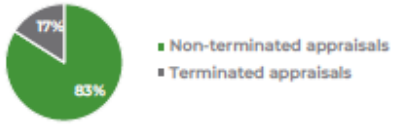
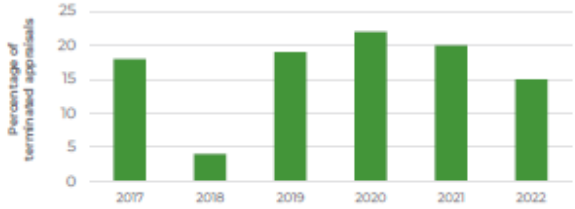


Figure 2: Percentage of terminated appraisals per year

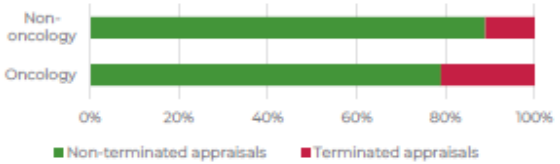


- Figure 3 illustrates the characteristics of terminated appraisals included in the analysis.
- 72% of terminated appraisals were for oncology products, and 35% were for combination drugs.
- All of the terminated combination drugs appraisals were oncology products.

Figure 3: Characteristics of terminated appraisals

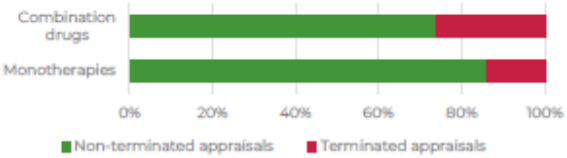
- Compared with appraisals for non-oncology products, oncology products were almost twice as likely to result in a terminated appraisal (11% vs 21%) (Figure 4).

Figure 4: Proportion of terminated appraisals for oncology and non-oncology drugs



- **As illustrated in Figure 5, a similar situation was also observed for monotherapies and combination drugs (14% vs 26%).**

Figure 5: Proportion of terminated appraisals for monotherapies and combination drugs



Discussion and Conclusion

- High acquisition cost coupled with high levels of uncertainty in the clinical data may reduce the likelihood of a product being deemed cost-effective, especially in oncology. Manufacturers may therefore be choosing not to commit the necessary resources to develop a submission, where the chance of success at the desired price point is low.
- In addition, oncology products are often approved for multiple indications. It is possible that manufacturers are choosing not to submit indications that would pull down the cost-effective price of higher-value indications. It would be interesting to determine what proportion of non-submissions are for products that already have NICE approval in a different indication.
- Given the need to include both the price of the new product and the price of the existing 'backbone' treatment there are significant challenges in demonstrating cost-effectiveness for combination treatments. It is therefore highly likely that combination products are less likely to be cost-effective than monotherapies and companies may be choosing not to submit to NICE when the clinical benefit of adding their therapy to existing therapy cannot justify the additional cost.

Abbreviations: HSTs: Highly Specialised Technologies; STAs: Single Technology Appraisals

References: 1 - https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/charging [Accessed 19/10/22]
2 - NICE, Guide to the processes of technology appraisal. Available at: https://www.nice.org.uk/media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf [Accessed 19/10/22]

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HPR17

Changing Landscape of Orphan Drug Reimbursement: Evidence from EU4 and England

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Introduction and Objective

- Orphan Drugs (ODs) are developed to treat rare, life-threatening or chronically debilitating conditions.
- While the European Medicines Agency (EMA) provides incentives to succour and accelerate the approval of Orphan Drugs (ODs) across the European Union,1 pricing and reimbursement (P&R) decisions and overall assessment timelines are subject to local country regulations. Reimbursement decisions are often driven by the outcomes of Health Technology Assessments (HTA) and pricing may be influenced by external reference pricing.
- These P&R differences can affect patient access, potentially creating significant disparities in the availability of new ODs across Europe.
- This study compares the rates of positive reimbursement decisions in Germany, England, France, Italy and Spain for ODs approved by the European Commission (EC) in 2015 and 2020 to determine whether timely patient access to Orphan Drugs (ODs) is improving in these five countries.

Methods

Figure 1: Methodology used in this research

- Time To Reimbursement (TTR) was calculated as a difference between the date of the national approval for reimbursement and the EC decision
- ODs that secured reimbursement after cut-off dates were not included in the TTR calculations to allow comparison across equal time periods
- In calculating the % reimbursement, only the drugs with their evaluation initiated before the time of performing analysis were included

Results

- 12 ODs approved by EMA in 2015 and 22 ODs approved in 2020 were identified. Their reimbursement status at the cut-off dates (June 2017 and June 2022 respectively) and median time to reimbursement in analysed countries are illustrated in Figures 2-7.

Figure 2: Median TTR for ODs approved by the EMA in 2015 and 2020

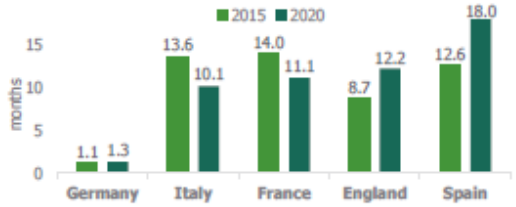
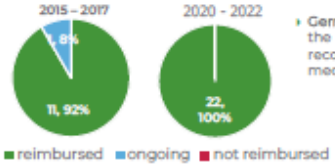
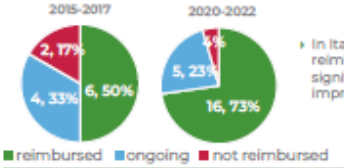


Figure 3: Reimbursement status of EMA-approved ODs in Germany



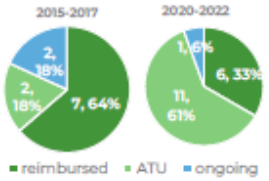
- Germany remained the country with the highest percentage of positive recommendations and the shortest median time to reimbursement.

Figure 4: Reimbursement status of EMA-approved ODs in Italy



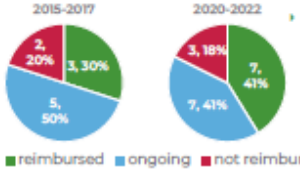
- In Italy, the percentage of positive reimbursement decisions increased significantly and median TTR improved.

Figure 5: Reimbursement status of EMA-approved ODs in France



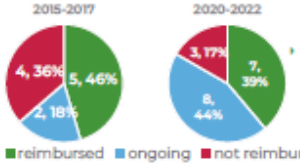
- In France, although a decrease in the percentage of reimbursed ODs has been noted, thanks to the implementation of Early Access program (ATU)2 patients could access respectively 82% (2017) and 94% (2022) of assessed ODs.

Figure 6: Reimbursement status of EMA-approved ODs in England



- The percentage of positive recommendations improved in England, with 3 out of 7 ODs from 2020 being approved through route for Highly Specialised Technologies (HST). However, a longer TTR than in previous years was noted.

Figure 7: Reimbursement status of EMA-approved ODs in Spain



- The percentage of positive recommendations decreased in Spain while the median TTR increased significantly between 2017 and 2022.

Discussion and Conclusion

- Despite the larger volume of ODs approved by EMA in 2020 than in 2015, the reimbursement ratio has increased in the majority of the countries examined, suggesting improving patient access to ODs. However, wide differences in reimbursement decisions and TTR timelines prevail.
- Germany continuously provides the most robust patient access to ODs due to the policy of automatic reimbursement of drugs with orphan designation and the strategy of not limiting access during the price negotiation process.
- The largest improvement in both ratio of approved ODs and the time to reimbursement can be seen in Italy. Progress in TTR corresponds with the legislative changes in the price negotiation process (which now imposes limitations to the clock stop) and COVID-19 mitigating strategies aimed to improve reimbursement decision-making.
- Despite the increased percentage of ODs in the ongoing price negotiation process, wide access to ODs is maintained in France owing to the implementation of the Early Access programme.
- In England, the increased percentage of positive reimbursement decisions coincides with the increased median TTR, presumably due to the higher volume of ODs in the reimbursement process.
- Analysis suggests that Spain, where the authorities frequently oppose reimbursement of medicines involving a major budget impact, remains the most challenging market.
- It is worth noting that one of the causes of the lengthier TTRs could be a delay in the manufacturer's choice to file a P&R dossier after the drug's EMA authorization, which is independent of local authorities.

*The national reimbursement dates for each product were collected from the official websites of the national agencies: Agenzia Italiana del Farmaco (AIFA), Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA), The National Institute for Health and Care Excellence (NICE) and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF)
ATU: Autorisation Temporaire d'Utilisation; EC: European Commission; HST: Highly specialised technology; EMA: European Medicines Agency; OD: Orphan Drug; P&R: pricing and reimbursement; TTR: Time to Reimbursement

References: 1. EMA, Orphan incentives. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives [Accessed 29/08/22] 2. Forster, A. (2022). Market access for medicines treating rare diseases: Association between specialised processes for orphan medicines and funding recommendations. Social Science &Amp; Medicine, 306, 115116. doi: 10.1016/j.socscimed.2022.115116

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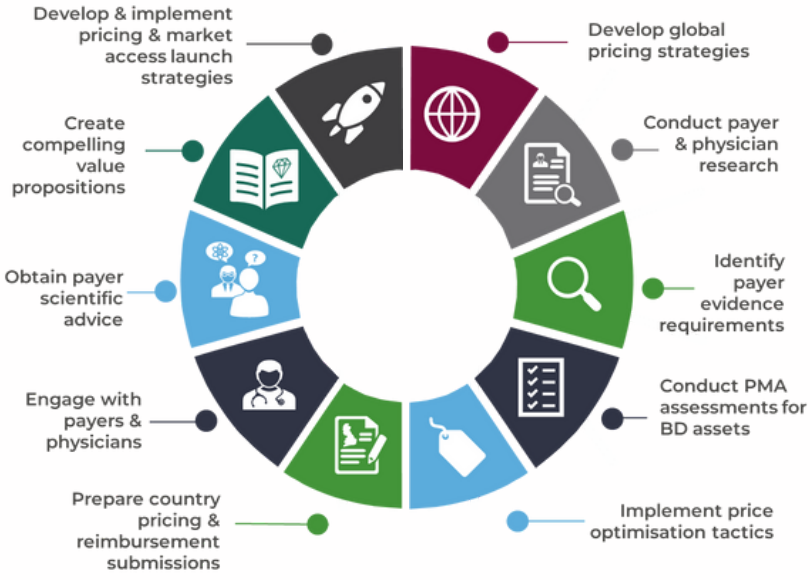

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