ORPH-VAL Principles in practice: Comparison of alignment of five European P&R systems

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1 Introduction

The introduction of European orphan drug legislation in 2000 was an acknowledgement of the major public health challenge of rare diseases. It has led to the development and approval of over 150 orphan medicinal products (OMPs). Yet many of these new products do not reach patients in time, leading to continued morbidity and/or loss of life or quality of life (Zamora et al. 2017). These delays in treating patients, which vary greatly from country to country, are in part due to inconsistencies across Europe in pricing and reimbursement (P&R) systems for rare disease treatments.

In an effort to improve consistency in P&R processes for OMPs, ORPH-VAL, a group of rare disease experts, undertook 18 months of work that resulted in the publication of its recommendations in the Orphanet Journal of Rare Diseases under the title: "*Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases*". These recommendations include nine principles that P&R processes for OMPs are suggested to align with in order to produce the best outcomes for all stakeholders involved.

In order to achieve better alignment across countries, the ORPH-VAL group believes it is necessary to first understand and explore where local P&R systems align with or diverge from the nine suggested principles. This report summarizes results of an assessment of individual country alignment with the principles, and what can be learned from this at both the country-level and the European-level.

It is important to highlight that this assessment does not look at how well countries are performing, or the outcomes of the P&R systems in these countries (i.e. speed or completeness of patient access to OMPs). It instead focuses on and explores the extent to which the P&R systems for OMPs in these countries are aligned with the ORPH-VAL recommendations. The authors recognize that good processes do not necessarily ensure good outcomes, and vice versa.

2 Methodology

The assessment was undertaken in England and Wales, France, Germany, Italy and Spain, and aimed to explore the level of alignment of individual country OMP pricing, reimbursement and funding processes with the nine ORPH-VAL principles.

The overall process involved three key steps:

1. A review of literature, country P&R guidelines, and process descriptions from publicly available sources in order to understand individual country processes and how they relate to each of the principles and their sub-principles. A database was created in Excel that included a description of how country processes align to each of the principles and sub-principles, with supporting references.

On this basis, a subjective assessment of the level of alignment with the nine principles was made. Alignment levels were categorised as "mostly aligns", "somewhat aligns" and "not

closely aligned". Alignment was assessed for each of the 16 sub-principles. This was done by one person and reviewed by a second person between July and October 2017.

2. Interviews were conducted with country experts from the ORPH-VAL Working Group between July and October 2017. One expert per country was interviewed. The objective was to review the interpretation of the country P&R processes and their relation to the principles and sub-principles. The interviewees received the database with the country assessment before the interview. The feedback received was primarily around clarifications on country processes. Assessments from step one were then updated with any new information.

3. Results were then presented to the ORPH-VAL Working Group and to industry representatives to gather additional insights between July and October 2017. Input was received from the French Industry Association (LEEM), the German Association of Research-Based Pharmaceutical Companies (VFA), and from the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), which was then further incorporated into the assessments.

Payer input was also received from representatives of the G-BA in Germany, HAS in France, and NICE and NHS England in UK through panel discussions during conference sessions (ISPOR Glasgow, 2017and WODC Barcelona, 2017). For both conferences, the format was broadly similar, starting with an overview of the principles, and a brief presentation of the comparison analysis in the selected countries by the moderator. The panellists were invited to respond to the analysis and discuss the areas of alignment or misalignment with the ORPH-VAL principles in their countries and the potential need for change.

The next section provides a high-level summary of the areas of alignment across the five countries included, indicated by a colour code (green mostly aligned, orange somewhat aligned, red mostly not aligned). Where there was disagreement amongst reviewers on the level of alignment, this is indicated by an asterisk. The following section provides some discussion on the findings and identifies trends within and between countries. The final section of the report provides the detailed assessments of the country systems and the rationale for the assessment of alignment.

It should be highlighted that this endeavour represents an exploration of an approach, rather than a definitive assessment. The methods used to determine alignment involved a small sample of reviewers and little formal validation was undertaken. The process of assessing alignment is fundamentally subjective, and reviewers' interpretation of the principles may not be consistent, making comparisons between countries potentially unreliable. This work should therefore be used to provoke debate, discussion and further exploration amongst interested stakeholders. Further research and multi-stakeholder validation is necessary.

3 Summary of assessment

	*Country system **mostly aligns** with principle*		*Country system **somewhat aligns** with principle*		*Country system is **not closely aligned** with principle*

** Consensus was not fully reached on assessment and/or alignment between stakeholders providing feedback*

Principle	Sub-Principle	Alignment					
		EN STA	EN HST	FR	DE	IT	ES
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework	Use of patients, healthcare system and wider society perspectives			*	*		
	Societal values underpinning value assessment are explicit						
	Use of MCDA frameworks approach			*			
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value	Reimbursement decisions should be based on product value			*	*		
	Price should be informed by price-value precedents for other specialist medicines						
	P&R status should be modulated to reflect other considerations (e.g.: societal preferences, rarity, budget impact and sustainability)				*		
	ICER thresholds (if applicable) should be modulated to reflect specificities of rare diseases				N/A		N/A
	Balance incentives for new research investment in rare diseases while maximising value for money for healthcare systems						
Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities	Assessment builds on EU decisions and recommendations	*	*				

EN: England and Wales; STA: Single technology appraisal; HST: Highly specialised technologies; FR: France; DE: Germany; ICER: Incremental cost-effectiveness ratio; MCDA: multi-criteria decision analysis; N/A: not applicable; OMP: Orphan medicinal product

Principle	Sub-Principle	Alignment					
		EN STA	EN HST	FR	DE	IT	ES
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives	Disease-specific expert physicians should be involved in the value assessment						
	Patients and their carers should be involved in the value assessment						
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.	Payers should consider uncertainty associated with rare diseases						
	Value assessment processes should be adaptive and continuous						
	P&R decisions should allow movement both up and down with newly generated evidence on value						
	Where adaptive processes are required, all parties need to agree on this iterative process						
	Collection and analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level	*		*			

EN: England; STA: Single technology appraisal; HST: Highly specialised technologies; FR: France; DE: Germany; HCP: Healthcare professional; OMP: Orphan medicinal product

Principle	Sub-Principle	Alignment					
		EN STA	EN HST	FR	DE	IT	ES
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations	All patients specified in the product license should receive access to treatment						
	Different decisions on access may apply to different sub-populations in which the OMP value substantially differs						
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs	National level coordination to avoid disparities in access between regions			*			
	Funding should come out of normal healthcare budgets rather than ear-marked rare disease funds						
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability	National collaboration to improve forecasting of expenditure and ensure adequate funding of OMPs			*			
	Early stage dialog between all stakeholders to ensure long term sustainability of outcomes						
Principle 9: In the future, there should be greater co-ordination of OMP value assessment processes at a European level	Collaborate with other European payers in regard to value assessment and data generation						

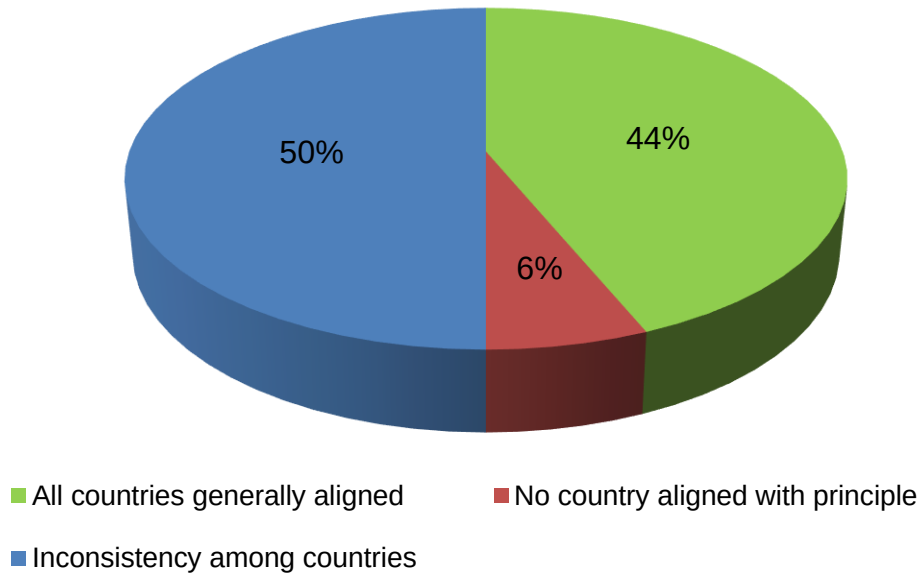
EN: England; STA: Single technology appraisal; HST: Highly specialised technologies; FR: France; DE: Germany; HTA: Health technology assessment; OMP: Orphan medicinal product

4 Discussion

The results of the assessment provided insight into where P&R systems of the investigated countries align with or diverge from the nine ORPH-VAL principles, or where there is uncertainty around alignment. Outlined below are trends between and across countries, as well as key insights within individual countries.

Cross-country trends: commonalities across countries on principles

There were seven sub-principles that all countries were generally aligned with (either mostly or somewhat aligned), one sub-principle that no country was aligned with at all, and eight sub-principles that countries were inconsistently aligned with (some fully, semi, or not at all aligned).



There are a number of areas where there is good alignment with the ORPH-VAL principles among countries, while other areas reveal inconsistent alignment.

The sub-principle regarding coordination at EU or international level of the collection and analysis of real world evidence was the only principle with no alignment in all of the study countries.

Based on the identified good and inconsistent alignment among countries on the nine principles (and 16 sub-principles), there are some areas in which greater alignment may be possible, and which may provide ideas for improving P&R processes for rare diseases.

(Sub) Principles with good alignment among countries	(Sub) Principles with inconsistent alignment among countries
P1: Use of patient, healthcare system and wider society perspectives P2: Decisions should be based on product value P4: Disease-specific expert physicians should be involved in the value assessment P5: Value assessment processes should be adaptive and continuous; P&R decisions should allow movement with new evidence; when adaptive processes required, all parties need to agree P6: Different decisions on access may apply to different sub-populations, in which the OMP value substantially differs P7: Funding should come out of normal healthcare budgets P9: Collaborate with other European payers	P1: Societal values underpinning value assessment are explicit P2: Price informed by price-value precedents for other specialist medicines; balance incentives for new research investment in rare diseases while maximising value for money for healthcare systems P3: Assessment builds on EU decisions P4: Patients and their carers should be involved in the value assessment P5: Payers should consider uncertainty associated with rare diseases P7: National level coordination to avoid disparities in access P8: Early stage dialog between all stakeholders to ensure long term sustainability of outcomes

Potential areas of focus at the EU level

The top five areas where efforts could be focused for possible increased alignment of rare disease P&R processes are outlined below.

Potential areas of focus at EU level
P1: Societal values underpinning value assessment should be explicit P3: Improved country motivation and requirement to build assessments based on EU decisions and recommendations may help create a more standardized process P4: Consistent patient and expert involvement, and analysis on actual influence of involvement on decision making to ensure best utilization of information from these key experts P5: Collection/analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level P5: Uncertainty as a key factor relating to OMPs should be a high priority for consideration

Country specific insights

Outlined below is a more in-depth view of each country, the areas in which they are aligned with the principles, and areas of misalignment.

England STA/HST

Areas of alignment	Areas of misalignment
P1 - Use of patients, healthcare system and wider society perspectives P1 - Societal values underpinning value assessment are explicit P4 - Involvement of disease-specific expert physicians	P2 - P&R decision: ICER thresholds should be modulated to reflect specificities of rare diseases P5 - To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time. P8 - Improved multi-stakeholder collaboration for forecasting and funding of OMPs

In England, the NICE HST pathway is the most adapted to OMP assessment with a comprehensive process that allows for a strong integration of the patient and the healthcare perspective (P1). In assessments, aspects such as the nature of the condition, impact of the technology and impact beyond health benefits are considered. The societal values underpinning the NICE process are also explicit, with a Citizen's Council providing clear guidance on issues relating to preferences for evaluating rare disease treatments (P1). In addition, NICE incorporates significant involvement of disease specific experts (HCPs) and patients as part of the submission *and* decision-making process (P4), although the impact of this involvement on the decision is sometimes questioned. This was corroborated during payer discussions at ISPOR and WODC conferences which highlighted the effort that NICE was expending to ensure the meaningful engagement of patients in the HTA process.

An area of possible improvement in alignment concerns ICER thresholds (P2). The Principles suggest that ICER thresholds should be modulated to reflect specificities of rare diseases, however this is only the case for the HST process at NICE, not the STA process. This leads to large 'steps' between ICER thresholds for medicines that may only differ slightly (e.g a prevalence of 450 versus 600 patients). A second area for improved alignment relates to how NICE deal with the inherent uncertainty that exists with OMPs. The Principles suggest that P&R processes should be adaptive to reflect data collected post approval, but currently relatively few medicines are subject to managed access agreements that incorporate an adaptive mechanism, especially where medicines are appraised through the STA pathway. One other possible area for improved alignment is around implementing better collaboration between manufacturers, NICE and payers at national-level, to improve forecasting tools of expenditure and ensure adequate funding of OMPs (P8). Currently, this is being done at the product level as part of the P&R process and negotiations.

France

Areas of alignment	Areas of misalignment
P4 - Patients and their carers should be involved in the value assessment P6 - All patients specified in the product license should receive access to treatment P7 - Funding should come out of normal healthcare budgets	P1 - Reference of how different elements of value are prioritised should be made more explicit, where societal and family burden should be recognised P5 - Uncertainty with OMPs should be considered P5 - Collection/analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level

In France, advances have been made in terms of involving patients and carers in the assessment (P4), following a new procedure introduced in 2017. Patient access and reimbursement is high, owing to the fact that once an OMP is approved, all patients within license usually receive access (P6), and these costs for reimbursement come entirely from national health insurance (P7). In terms of possible improved alignments, it is currently unclear to what extent the different elements of value influence the final outcome (P1). More transparency is needed around this. When assessing the criteria considered, societal or family and carer burden have little or no weight, despite being important aspects of the provision of care of rare disease patients (P1). It is also currently unclear if and how uncertainty is considered in the assessment (P5). The collection/analysis of real-world data co-ordinated at a EU or international level is recommended, as currently only France specific data is considered (P5). Despite possible improved alignments, patient access in France is very good, highlighting the fact that processes do not always guarantee good outcomes, and further efforts to examine and align good processes with good outcomes are still needed.

Germany

Areas of alignment	Areas of misalignment
P2 - Decisions should be based on product value P2 - Pricing and reimbursement decisions should be founded on the assessment of OMP value and adjusted to reflect other considerations beyond product value. P3 - Assessment should build on EU decisions and recommendations	P1 - Societal values underpinning value assessment should be explicit P4 - Patients and their carers should be involved in the value assessment P5 - Collection/analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level

In Germany P&R decisions are primarily based on product clinical value (P2), a point that was also mentioned by payers in discussions during the conference panel debates. Moreover, Germany is one of the only countries that builds its assessments on EU recommendations, by explicitly referencing COMP (P3). Patient access to OMPs is excellent in Germany, reflecting immediate reimbursement of medicines at the time of launch and a process that includes adaptation to orphan specificities (P2).

Some possible areas to improve alignment include that societal values included in the assessment are only somewhat explicit (P1). Patients and their carers are involved to some extent in the value assessment process, but their influence in the decision-making process appears to be limited (P4). The collection/analysis of real-world data co-ordinated at a EU or international level is recommended, as currently only German specific data is considered (P5). These findings were supported by input from payer discussions at the conference panel debates, which highlighted that a significant gap exists concerning collection of registry and real-world data.

Italy

Areas of alignment	Areas of misalignment
P1 - Use of patients, healthcare system and wider society perspectives P2 - Decisions should be based on product value P7 - Funding should come out of normal healthcare budgets	P4 - Involvement of disease-specific expert physicians P5 - Collection/analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level P6 - All patients specified in the product license should receive access to treatment

Italy incorporates a strong integration of patient and healthcare perspectives in assessment (P1), and makes decisions primarily based on product clinical value (considering therapeutic value, level of innovation, and alternatives) (P2). Once accepted for reimbursement, OMPs are funded from national budgets (P7). While disease specific experts are included to some extent in the assessment, stakeholders are involved in various phases of HTA in only five of the 11 regions in which it is regulated, and involvement elsewhere is not formalized (P4), which suggests an area for potential improved alignment. The collection/analysis of real-world data co-ordinated at an EU or international level is suggested, as currently registries are national and not shared with other EU countries (P5). This point was also raised by payers, who commented that a main challenge for all countries is negotiating real-world data collection and defining how these tie to reimbursement. At times, reimbursement may be restricted to certain populations, although ideally reimbursement would be available to all patients with license (P6).

Spain

Areas of alignment	Areas of misalignment
P1 - Use of patients, healthcare system and wider society perspectives P5 - P&R processes should allow movement with evidence P5 - Uncertainty with OMPs should be considered	P4 - Involvement of disease-specific expert physicians P5 - Collection/analysis of real-world data (registries & databases) should be co-ordinated at a EU or international level P7 - Funding should come out of normal healthcare budgets

Spain incorporates patient and healthcare perspectives in OMP assessment (P1). It allows movement with evidence, by utilizing MEAs and payment-by-results at regional levels (P5) and considers uncertainty with OMPs by allowing flexible criteria to account for these uncertainties (P5). While disease specific experts in Catalonia (patients, carers, physicians & geneticists) participate in discussions, at a national level patient involvement is largely restricted (P4), suggesting a potential area for improved alignment. The collection/analysis of real-world data co-ordinated at a EU or international level is recommended, as currently registries are regional and national only (P5). There is variation across regions on real prices and payment methods, which may create regional disparities in access to OMPs (P7).

Study limitations

Some overall limitations of the assessment that should be acknowledged include the following:

- HTA guidelines and processes were reviewed, and a targeted literature review was conducted for research papers that illustrated a given topic. Publicly available sources, and country guidelines and process descriptions were relied upon to obtain this information, thus, the latest changes or discussions may not have been captured. Moreover, processes may have evolved or changed since this assessment. Even so, the results remain useful to foster discussions around the specific topics of interest within and across countries. These potential new processes will provide good examples of how countries are implementing change.
- The alignment of country processes with the principles relied on the authors' and reviewers' understanding of the processes, and interpretation of how those processes align with the principles. Several rounds of feedback were received in order to minimise any potential misinterpretations of the country processes.
- The assessment relied on concrete information and the authors tried to ensure consistency of the approach as much as possible, but inconsistencies were present - for example, at times reviewers from the different countries expressed differing perspectives from each other - and the assessments are still, in and of themselves, subjective.

- Assessments were reviewed by ORPH-VAL country experts to 1) validate the authors' understanding of the process and provide additional information where data gaps remained, and 2) validate the subjective assessment of level of alignment. In most cases, however, these experts were not the policy makers involved in P&R processes and may not have had full knowledge of these processes.
- Only five countries were included in the analysis, so it is not possible to provide a broader view of all EU countries with special OMP processes.
- The assessment focused on alignment of country P&R processes for OMPs with the ORPH-VAL recommendations, not on outcomes. The results of this assessment are thus not conclusive, but rather a stimulant for discussion and next steps.

Summary and next steps

The task of improving reimbursement processes for OMPs is significant and important. The ORPH-VAL Principles represent a basis upon which stakeholders within countries can discuss the optimal process for assessing and reimbursing these medicines, and a route towards greater consistency in approach across Europe.

The review of five countries and their alignment (or lack of alignment) with the nine principles points to possible next steps for process improvement. These areas of focus could be on better and more effective patient involvement in decision making, better and more systematic balancing of incentives, stronger methods of taking uncertainty into account, and finding tangible solutions for collecting real world data at the EU level. Moreover, further research on the links between good process and good outcomes should be conducted in the near future to further validate and consolidate findings. These assessments are not intended to be conclusive but rather a stimulant for further discussions and recommendations on possible next steps. It is evident that countries are making strides in improving OMP processes, and at the same time there are areas that could be focused upon in order to further refine these processes and establish effective systems at both national and international levels.

5 Individual country assessments

	Consensus was not fully reached on assessment and/or alignment between stakeholders providing feedback		Sub-principles where variability of interpretation exist across countries

5.1 England

Sub-Principle	Comment	Alignment	References
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework			
Decision-makers should consider OMP value from the perspective of patients, the healthcare system and wider society	NHS is the final decision maker and takes advice from NICE as part of the following processes **STA** Patient and healthcare system level elements are mostly incorporated into the Single Technology Appraisal (STA) processes. No real consideration of societal impact of the disease and treatment. **HST** Patient and healthcare system level elements are mostly incorporated into the Highly Specialised Technology (HST) programme. HST process considers societal impact of the disease and treatment.	STA: Somewhat HST: Mostly	(NICE, 2009, 2017e)
Core elements of value and other considerations (See separate Table)		STA: Somewhat HST: Mostly	
Societal values underpinning value assessment are explicit?	Principles that NICE should follow in designing processes/developing guidance have been produced by NICE, in part informed by the Citizen's Council. These principles include positioning on societal aspects such as equality, morality, discrimination, rare disease, rule of rescue etc.	Mostly	(NICE, 2008)
Use of multi-criteria decision analytic (MCDA) frameworks approach?	**STA** Committee considers clinical and cost-effectiveness only and decisions are driver by ICERs. **HST**	STA: Not closely HST: Somewhat	(NICE, 2009, 2017e)

	Committee considers aspects of nature of the condition, value for money, impact of the technology beyond direct health benefit, in addition to the clinical and cost-effectiveness. Increasingly, with introduction of explicit ICER thresholds, the process is moving away from MCDA.		
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value			
Reimbursement decisions should be based on product value	For both the STA and HST route, the clinical and cost-effectiveness are key drivers of the decision.	Mostly	(NICE, 2009, 2017e)
Price should be informed by price-value precedents for other specialist medicines	NICE HST used to explicitly compare value for money with other ultra-OMPs, now it is cost-effectiveness. In STA price is determined by cost effectiveness alone (vs standard of care in same disease area).	Not closely	(NICE, 2013b, 2016a, 2017d)
Beyond product value, price and reimbursement status should be modulated to reflect other considerations, such as societal preferences, rarity, budget impact and sustainability of innovation in rare diseases (See Table 2)	**STA** In STA cost effectiveness is the major decision driver. Social value principles state that orphan drugs should be treated in the same way as any other treatment, and there is no adoption of 'rule of rescue' beyond other social principles on promoting equality. **HST** In HST process budget impact and rarity (and associated challenges in recouping investment) have been considered within decisions to date. Broader societal benefits are considered informally.	STA: Not closely HST: Somewhat	(NICE, 2008, 2013b, 2015a, 2015b, 2016a, 2017b, 2017c, 2017d)
If cost-effectiveness is applied, ICER thresholds should be modulated to reflect specificities of rare diseases	In HST programme (ultra-orphan), an ICER range of £100k to £300k is considered, whereas in STA, a threshold ICER of £20-30k is considered or up to £50k if end of life criteria applies. For STA reviews, ICERs are not modulated to reflect specificities of rare diseases.	STA: Not closely HST: Somewhat	(NICE, 2008, 2017e)
Balances incentives for new research investment in rare diseases while maximising value for money for healthcare systems	Many OMPs have not been recommended for use in the UK (20% of orphan medicines with marketing authorisation have been assessed by HTA; 65% of those have received reimbursement); prices of medicines are lower than in other countries with similar GDP per capita (exchange rates have amplified this trend); total pharmaceutical spending as % of GDP is also lower than in other countries with similar GDP per capita (UK 1.2; France Germany and Italy 1.6; UK 2.1). However, in the HST process, R&D incentives are more explicitly recognised and price negotiations have explored return on investment.	STA: Not closely HST: Somewhat	(Kawalec, Sagan, & Pilc, 2016; OECD data, 2015; Vogler, Kilpatrick, & Babar, 2015)

Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities			
Assessment builds on the decisions and recommendations at a European level	NICE undertakes assessment from first principles with little explicit reference to European level assessments. Comments from reviewers: • EU level decision (EMA + EPAR) is of high relevance • however, HST does look at far more data than EPAR	Somewhat	(NICE, 2013a)
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives			
Disease-specific expert physicians should be involved in the value assessment and provide direct input	Significant involvement of HCP both as part of the submission process and in the decision-making process.	Mostly	(NICE, 2013a)
Patients and their carers should be involved in the value assessment in the following ways: - Systematic representation of patient associations in meetings that assess and appraise OMPs - Disease-specific patient representatives should be involved throughout the process and given appropriate training and support to contribute fully	Significant involvement of patient representatives both as part of the submission process and in the decision-making process. Patients are invited to submit evidence, take part in the evaluation committee meetings and can contribute to the discussion.	Mostly	(NICE, 2009, 2017e)
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.			
Payers should consider uncertainty in light of disease prevalence, disease severity and unmet need, amount of prior research conducted in the disease, extent to which the manufacturer has taken reasonable steps to minimise uncertainty.	**STA** The different ICER assumptions are reflective of the uncertainties. Given ICERs are an important driver in NICE decisions, the range of uncertainty results in usage restrictions and recommendations. **HST** The HST process has historically been more accommodating to evidential uncertainty. HST allows for higher ICER thresholds to reflect the uncertainties associated with OMPs.	STA: Not closely HST: Mostly	(Cerri, Knapp, & Fernandez, 2014; Dakin et al., 2014; NICE, 2015a, 2015b, 2016a, 2017b, 2017c, 2017d)

Value assessment processes should be adaptive and continuous	When NICE publishes STA or HST guidance, a date is set for review where, in theory, the P&R status can be changed. Guidance may be reviewed before the review date when there is significant new evidence that is likely to change the recommendations. **HST** HST decisions have incorporated adaptive assessments and evidence generation through Managed Access Agreements (MAA) that have specified time periods until review and include P&R agreements that reflect evidence collected during contract period.	STA: Somewhat HST: Mostly	(NICE, 2009, 2015b, 2016a, 2017e)
P&R decisions should allow movement both up and down with newly generated evidence on value	NHS has the mandate on pricing and prices can be adjusted when new evidence becomes available through new PAS.	Somewhat	(NICE, 2017a)
Where adaptive processes are required, all parties (payers, HTA agencies, involved HCP, patients and industry) need to agree on this iterative process	**STA** Patient access schemes (PAS) are reviewed and agreed between the manufacturer and PASLU; PASLU is a multi-stakeholder group convened when necessary to agree whether the PAS is possible within the NHS - not necessarily to agree that it should be accepted. **HST** The MAA process involves all stakeholders (NICE, NHS England, manufacturer, clinical expert, patient organisation).	STA: somewhat HST: Mostly	(NICE, 2015c, 2016b, 2017f, 2017g)
Where possible, the collection and analysis of real-world data should be co-ordinated at a European or international level and should be integrated in disease level registries and databases	NICE requests UK specific data capture; if data on effectiveness comes from outside the UK, this is considered a deficiency.	Not closely	(NICE, 2013a)
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations			
Wherever possible, reimbursement decisions should seek to ensure that all patients specified in the product license should receive access to treatment	NICE STA and HST very commonly restrict reimbursement to sub-groups.	Not closely	(NICE, 2009, 2017a, 2017e)
Reimbursement may be reflective of situations where there is a broad spectrum of disease and clearly defined patient		Mostly	

subgroups in which OMP value substantially differs			
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs			
Funding for OMPs should be co-ordinated at a national level in order to avoid disparities in access between regions	**STA** CCG/regional specialised commissioning fund medicines, but legally mandated to by NICE (i.e locally funded, but through national coordination). **HST** Rare disease treatments assessed via the HST route are funded nationally via NHS commissioning.	STA: Mostly HST: Mostly	(NHS Clinical Commissioners, 2017; NHS England, 2017a, 2017b)
It is preferable that funding for OMPs should come out of normal healthcare budgets rather than from ear-marked rare disease funds that do not allow for a long-term perspective	Specialised treatments are all commissioned centrally through the NHS.	Mostly	(NHS Clinical Commissioners, 2017; NHS England, 2017a, 2017b)
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability			
Manufacturers, payers and HTA agencies should collaborate nationally to improve forecasting of expenditure and ensure adequate funding of OMPs	Forecasts for expenditure are done at the *product level* as part of the P&R process and negotiations. Negotiations with the NHS translate into collaborative agreements for specified amount of time. ABPI negotiates PPRS at the aggregate level on 4 yearly basis, including total cost forecasting.	Somewhat	(NICE, 2013a)
Early stage dialog between all stakeholders should be put in place to ensure long term sustainability of outcomes	NICE provides early scientific advice, a fee-for service consultation for manufacturers. The Office for Market Access is also available for less detailed discussions (under a pay for service consultation). NHSE has "specialised commissioning surgeries" for companies to discuss upcoming products at any stage.	Mostly	(NICE, 2017h)
Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level			
Collaborate with other European payers in regard to value assessment and data generation	HAS (France), IQWiG (Germany) and NICE (UK) are among the lead partners of the EUnetHTA Joint Action 3 which aims to define and implement sustainable model for the scientific and technical cooperation on HTA. However, no evidence that this has any impact on individual drug decisions.	Somewhat	(EUnetHTA, 2016)

5.2 France

Sub-Principle	Comment	Alignment	References
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework			
Decision-makers should consider OMP value from the perspective of patients, the healthcare system and wider society	Value elements used in France are mostly aligned with the core elements in the principles at the patient level (with the exception of patient economic burden from the disease). Elements proposed at the Healthcare System and Societal Level are not used as part of the Transparency Committee assessment of product benefit, but are sometimes relevant to the price negotiation process at CEPS. Impact on productivity are not explicitly considered by appraisal committees.	Somewhat	(HAS, 2017c)
Core elements of value and other considerations (See separate Table)		Somewhat	(HAS, 2017c)
Societal values underpinning value assessment are explicit?	TC will look at whether the new drug is beneficial for the public health; in terms of disease burden, mortality, morbidity, handicap and after-effects, quality of life and organisation of the care pathway. However, societal value is not considered, and the public health benefit is a clinically driven process. All OMPs are given a "low public health benefit" given the few patients affected. Underpinning societal values are somewhat transparent through the decision making factors used to inform SMR and ASMR which are clear from evaluation reports published by HAS.	Somewhat	(HAS, 2017c)
Use of multi-criteria decision analytic (MCDA) frameworks approach?	No formal MCDA approach, however Transparency Committee looks at multiple considerations, but decision is mainly influenced by clinical data only.	Somewhat	
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value			
Reimbursement decisions should be based on product value	Reimbursement decision is based on the SMR ratings which reflect product clinical value (economic and societal values do not contribute to the SMR level).	Mostly	(Ministère des Solidarités et de la Santé, 2016)

Price should be informed by price-value precedents for other specialist medicines	Prices are usually considered relative to other treatments in same disease area. In OMPs, it appears likely that informal price comparisons are undertaken with similar medicines in other disease areas. Other factors influence OMPs pricing: as part of the accord cadres, there is an arbitrary turnover threshold that is put in place (€50k per patient per year).	Somewhat	(Ministère des Solidarités et de la Santé, 2016; Sécurité sociale, 2017; Service-Public.fr, 2017)
Beyond product value, price and reimbursement status should be modulated to reflect other considerations, such as societal preferences, rarity, budget impact and sustainability of innovation in rare diseases (See Table 2)	Reimbursement is exclusively determined by the SMR. Pricing is on the other hand determined by the ASMR rating. In rare diseases, OMPs are typically granted ASMR IV or V as a result of the weaker trial methodology compared to more common diseases due to the small patient population. Other factors are considered by CEPS in pricing negotiations, including patient population size and budget impact. There is currently no alternative approach for OMPs to reflect the inherent uncertainty/ complexity of OMPs.	Somewhat	(Ministère des Solidarités et de la Santé, 2016)
If cost-effectiveness is applied, ICER thresholds should be modulated to reflect specificities of rare diseases	Cost effectiveness analysis is used within pricing negotiations for some products (ASMR III or higher; sales greater than EUR20m), but no explicit ICER thresholds are defined. It is unclear whether rare disease specificities are considered when interpreting the ICER. CEPS rather uses a budget impact analysis, and would accept price proposed for annual cost per patient not exceeding €50k if the price is in line with international prices. Currently ICERs are not adapted to reflect the inherent uncertainty/complexity of OMPs.	Not closely	(Ministère des Solidarités et de la Santé, 2015b)
Balances incentives for new research investment in rare diseases while maximising value for money for healthcare systems	The French system has historically allowed a high degree of access to innovative OMPs while using price-volume agreements and performance agreement to manage total expenditure. However, this appears to be changing in the last few years as many OMPs get ASMR V.	Mostly	(HAS, 2017a; Ministère des Solidarités et de la Santé, 2015b)
Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities			
Assessment builds on the decisions and recommendations at a European level	EPAR is reviewed by the Transparency Committee but is not the major driver of decisions.	Somewhat	(HAS, 2017e)
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives			

Disease-specific expert physicians should be involved in the value assessment and provide direct input	There are no rare disease specialists as part of the Transparency Committee members. However, disease-specific experts are invited by the TC to assess OMPs and provide their opinion on the reimbursement requests. Their contribution consists of an oral presentation summarising their feedback on the product being assessed based on their knowledge of the disease.	Mostly	
Patients and their carers should be involved in the value assessment in the following ways: - Systematic representation of patient associations in meetings that assess and appraise OMPs - Disease-specific patient representatives should be involved throughout the process and given appropriate training and support to contribute fully	A new procedure (Sept 2017) has recently been implemented where there is greater patient involvement. Patient associations are invited to contribute the OMPs assessment, they have the opportunity to complete a document summarising their experience of the disease. There is no visibility yet on this new procedure and how it is implemented in practice.	Somewhat	(Ministère des Solidarités et de la Santé, 2015a) (HAS, 2017d)
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.			
Payers should consider uncertainty in light of disease prevalence, disease severity and unmet need, amount of prior research conducted in the disease, extent to which the manufacturer has taken reasonable steps to minimise uncertainty.	Unclear whether any consideration is explicitly given to the level of knowledge in the disease and small patient population. Transparency Committee has been reluctant to accept the relevance of surrogate endpoints in rare diseases where there is not clear evidence of a correlation with improvement in outcomes.	Somewhat	(HAS, 2013c, 2017f)
Value assessment processes should be adaptive and continuous	Medicines are re-reviewed every 5 years, HAS also requests additional evidence generation or results from observational studies to re-assess ASMR level within a given time frame (1, 2 or 3 years) which is frequent for OMPs.	Mostly?	(HAS, 2013d, 2015, 2017g)
P&R decisions should allow movement both up and down with newly generated evidence on value	Prices are revised over time but regulation systems remain unclear, historically prices have only ever been lowered after re-evaluation.	Somewhat	

Where adaptive processes are required, all parties (payers, HTA agencies, involved HCP, patients and industry) need to agree on this iterative process	A legal framework is in place in France: the company and CEPS sign a contract which states the framework of the agreement. These kinds of contracts are established for financial based agreements and typically include the payer and the company only. However, there is no clear/specific methodology to support the reassessments and other stakeholders are not involved.	Somewhat	(Ministère des Solidarités et de la Santé, 2015b)
Where possible, the collection and analysis of real-world data should be co-ordinated at a European or international level and should be integrated in disease level registries and databases	Request France-specific data capture. There is no international coordination of real-world data collected.	Not closely	(HAS, 2017b; Ministère des Solidarités et de la Santé, 2015d)
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations			
Wherever possible, reimbursement decisions should seek to ensure that all patients specified in the product license should receive access to treatment	All patients within licence are usually considered.	Mostly	(Ministère des Solidarités et de la Santé, 2015c)
Reimbursement may be reflective of situations where there is a broad spectrum of disease and clearly defined patient subgroups in which OMP value substantially differs		Somewhat	
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs			
Funding for OMPs should be co-ordinated at a national level in order to avoid disparities in access between regions	Yes, there are 131 national reference centers for rare diseases working closely with 502 competence centers, that are closer to patients. There could potentially be some disparities between hospitals for products not included in the 'liste en sus' or that have been removed from the list.	Mostly	(Hopital.fr, 2015)
It is preferable that funding for OMPs should come out of normal healthcare budgets rather than from ear-marked rare disease funds that do not allow for a long-term perspective	Yes, and health costs are 100% reimbursed by the national health insurance for long-term disease (ALD).	Mostly	(Ameli.fr, 2008, 2017; Hopital.fr, 2015)
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability			

Manufacturers, payers and HTA agencies should collaborate nationally to improve forecasting of expenditure and ensure adequate funding of OMPs	Forecasts for expenditure are done at the product level as part of the P&R process, but there is no apparent collaboration between payers and industry for aggregate OMP cost.	Not closely	
Early stage dialog between all stakeholders should be put in place to ensure long term sustainability of outcomes	Early meetings with HAS before Phase III trial is possible – however these occur slightly late to allow sufficient time to put in the place all the complementary studies requested by HAS.	Mostly	(HAS, 2013a, 2013b)
Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level			
Collaborate with other European payers in regard to value assessment and data generation	HAS (France), IQWiG (Germany) and NICE (UK) are among the lead partners of the EUnetHTA Joint Action 3 which aims to define and implement sustainable model for the scientific and technical cooperation on HTA. However, these have a very limited impact on individual product decisions.	Somewhat	(EUnetHTA, 2016)

5.3 Germany

Sub-Principle	Comment	Alignment	References
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework			
Decision-makers should consider OMP value from the perspective of patients, the healthcare system and wider society	Patient level elements are considered with a focus on the magnitude of the clinical benefit. Impact on patients' morbidity and HRQOL are key areas of consideration. Healthcare system benefits and societal benefits are taken into considerations. Public health benefit value is not considered. However, manufacturer dossiers need to include information on the expected number of patients and patient groups for which an added benefit exists as well as costs for the public health system (statutory health insurance). Ethical considerations are also sometimes implicitly used in appraisals Social productivity is considered: productivity loss due to incapacity as part of the cost side, productivity loss due to mortality as part of the benefit side (no unpaid work, e.g. housework). All direct costs have to be considered, including both medical and non-medical (when applicable), whereas indirect costs are not a primary consideration but can be evaluated separately if they are substantial, with productivity losses due to incapacity being included only on the cost side.	Somewhat	(Fischer, Heisser, & Stargardt, 2016; Fischer & Stargardt, 2014; G-Ba; G-Ba; G-Ba, 2015, 2017; G-Ba., 2017; IQWiG; IQWiG; ISPOR, 2014; Lauenroth & Stargardt, 2017; LSE, 2017; Thokala et al., 2016; WHO, 2013a)
Core elements of value and other considerations (See separate Table)		Mostly	
Societal values underpinning value assessment are explicit?		Somewhat	
Use of multi-criteria decision analytic (MCDA) frameworks approach?	The G-BA approach to establishing the degree of added benefit is a simple form of MCDA, but it only considers clinical value domains. Also, G-BA has an explicit categorical rating for degree of uncertainty of evidence considered.	Somewhat	(Fischer & Stargardt, 2014; LSE, 2017; Thokala et al., 2016; Wahlster, 2013)
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value			
Reimbursement decisions should be based on product value	Reimbursement and rebate levels determined by level of additional benefit of treatment, i.e. based on clinical value of the product mainly.	Mostly	(G-Ba; WHO, 2013b)

Price should be informed by price-value precedents for other specialist medicines	Prices are usually set relative to other medicines in the same disease area. However, for OMPs prices in other diseases are likely relevant to rebate negotiations.	Somewhat	(Dehnen, Goldhagen, Schmöller, & Wörmann, 2013; Lauenroth & Stargardt, 2017; Mueller, Schmidt, Schrank, & Neeser, 2015; Theidel & von der Schulenburg, 2016)
Beyond product value, price and reimbursement status should be modulated to reflect other considerations, such as societal preferences, rarity, budget impact and sustainability of innovation in rare diseases (See Table 2)	Patient population size and budget impact is considered by Sick Funds when negotiating rebate. No explicit process for incorporating societal preferences or sustainability of innovation in rare diseases during appraisal. However, on the other hand, orphan drugs have a special treatment from G-BA, at least some benefit is assumed so already avoid situation when price is set at the level of comparators.	Somewhat	(G-Ba; G-Ba)
If cost-effectiveness is applied, ICER thresholds should be modulated to reflect specificities of rare diseases	Cost-benefit-analysis (CBA) is not standard practice in the evaluation, but, rather, is optional and can be initiated if no agreement is reached between sickness funds and the manufacturer on the price premium, or if the manufacturer does not agree with the decision of the G-BA regarding premium pricing (added benefit).	Not applicable	(Fischer et al., 2016; G-Ba; LSE, 2017; WHO, 2013b)
Balances incentives for new research investment in rare diseases while maximising value for money for healthcare systems	There is a high level of patient access to innovative OMPs in Germany; Sick Funds have successfully negotiated substantial discounts following G-BA assessment. A lot of investment into research in rare diseases by public sector.	Mostly	(Bouslouk, 2016; Gammie, 2015; Kawalec et al., 2016)
Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities			
Assessment builds on the decisions and recommendations at a European level	Yes – COMP decision explicitly referenced.	Mostly	(G-Ba)
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives			

Disease-specific expert physicians should be involved in the value assessment and provide direct input	HCPs are involved in G-BA assessment.	Mostly	
Patients and their carers should be involved in the value assessment in the following ways: - Systematic representation of patient associations in meetings that assess and appraise OMPs - Disease-specific patient representatives should be involved throughout the process and given appropriate training and support to contribute fully	An over-arching patient association is involved in the assessment and their argument are considered by the GBA in the decision making. Certain disease-specific patient associations are entitled to appoint patient representative to the GBA. Patient representatives that come from consumer protection agencies are also invited. Overall patient representatives appear to have limited influence in the decision-making process.	Somewhat	(G-Ba; G-Ba)
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.			
Payers should consider uncertainty in light of disease prevalence, disease severity and unmet need, amount of prior research conducted in the disease, extent to which the manufacturer has taken reasonable steps to minimise uncertainty.	The special case of orphan drugs: ".... Orphan drugs have a special status in the early benefit assessments of pharmaceuticals with new active ingredients. In accordance with statutory requirements (SGB V, section 35a, paragraph 1, sentence 10) the additional medical benefit of these medications is already proved through market authorization...In principle, this statutory provision assumes an additional benefit for the orphan drug authorized. ..."	Somewhat	(G-Ba; IQWiG, 2017; Kirchmann, Kielhorn-Schönermark, & Schönermark, 2017; Medic et al., 2017; Theidel & von der Schulenburg, 2016)
Value assessment processes should be adaptive and continuous	Yes, in certain circumstances. GBA sets an expiry date for some decisions and review the evidence after this set time.	Somewhat	(GKV, 2017)
P&R decisions should allow movement both up and down with newly generated evidence on value	Companies can apply for a renewed benefit evaluation if new scientific findings are available. Price increase Jakavi case: Once €50 M annual budget threshold was exceeded, IQWIG was commissioned to evaluate a new Jakavi dossier in 2014 and Jakavi improved its benefit from minor to considerable. There was a price increase between 2014 and 2015.	Mostly	(G-Ba; WHO, 2013b)

Where adaptive processes are required, all parties (payers, HTA agencies, involved HCP, patients and industry) need to agree on this iterative process	Managed entry agreements are rarely used in Germany. However, as re-evaluations from re-submissions follow the same process as per new products, HTA, HCPs, patients and industry are all involved.	Somewhat	(GKV, 2017; LSE, 2017; Pauwels, Huys, Vogler, Casteels, & Simoens, 2017)
Where possible, the collection and analysis of real-world data should be co-ordinated at a European or international level and should be integrated in disease level registries and databases	German epidemiology data and applicability of efficacy study results to German situation are requested. Refer to EMA decisions if requirement is set at regulatory level and set the time limit in accordance to date when new data is expected.	Not closely	(Ecker, Art, Fink, & Ecker, 2015; G-Ba, 2013; SKC, 2017)
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations			
Wherever possible, reimbursement decisions should seek to ensure that all patients specified in the product license should receive access to treatment	Sub-groups can be assessed separately for value but all patients are included in reimbursement.	Mostly	(LSE, 2017)
Reimbursement may be reflective of situations where there is a broad spectrum of disease and clearly defined patient subgroups in which OMP value substantially differs		Somewhat	(LSE, 2017)
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs			
Funding for OMPs should be co-ordinated at a national level in order to avoid disparities in access between regions	G-BA makes decisions centrally on which services of the medical care are taken over by the statutory health insurance (GKV). Nearly 90% of the population are insured by one of the roughly 130 statutory health insurance ("SHI") funds and around 9% are insured by private insurance companies. SHI are represented by a single national head organisation GKV-SV.	Mostly	(G-Ba; G-Ba)
It is preferable that funding for OMPs should come out of normal healthcare budgets rather than from ear-marked rare disease funds that do not allow for a long-term perspective		Mostly	(G-Ba; G-Ba)
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability			
Manufacturers, payers and HTA agencies should collaborate nationally to improve forecasting of expenditure and ensure adequate funding of OMPs	Forecasts for expenditure are done at the product level as part of the P&R process at the time of assessment and re-assessment, but there is no apparent collaboration between payers and industry for aggregate OMP cost.	Not closely	

Early stage dialog between all stakeholders should be put in place to ensure long term sustainability of outcomes	Yes – manufacturers can engage with GBA to obtain an early fee for service scientific advice.	Mostly	(G-Ba)
Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level			
Collaborate with other European payers in regard to value assessment and data generation	HAS (France), IQWiG (Germany) and NICE (UK) are among the lead partners of the EUnetHTA Joint Action 3 which aims to define and implement sustainable model for the scientific and technical cooperation on HTA. G-BA was the second after NICE in number of parallel -EMA -HTA advice (non- SEED) given until 2015. However, it is not clear if EUnetHTA assessments influence individual G-BA decisions.	Somewhat	(EMA, 2016; EUnetHTA, 2016; European Commission, 2017a, 2017b)

5.4 Italy

Sub-Principle	Comment	Alignment	References
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework			
Decision-makers should consider OMP value from the perspective of patients, the healthcare system and wider society	The key value drivers are the disease profile (disease severity and burden + unmet need), the product profile (therapeutic value + level of innovation + therapeutic alternatives), and the economic context (price of alternatives + budget impact).	Mostly	(Folino-Gallo, Montilla, Bruzzone, & Martini, 2008; The Economist Intelligence Unit, 2015)
Core elements of value and other considerations (See Table 2 below)		Mostly	(Folino-Gallo et al., 2008; The Economist Intelligence Unit, 2015)
Societal values underpinning value assessment are explicit?	There are some general statements from the Ministry of Health highlighting the need to develop new OMPs, but this has not translated into explicit criteria during the assessment. There is also a limited perception from society on the value of OMPs.	Not closely	(AIFA)
Use of multi-criteria decision analytic (MCDA) frameworks approach?	An algorithm is used to assign the degree of innovation for drugs in which the 3 evaluated parameters are: (i) unmet therapeutic need, (ii) added therapeutic value and (iii) quality of evidence.	Somewhat	(AIFA, 2017)
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value			
Reimbursement decisions should be based on product value	The product profile (therapeutic value + level of innovation + therapeutic alternatives) is one of the pillars used by AIFA in reimbursement decisions - there is a high level of emphasize on product innovation.	Mostly	(Garau & Mestre-Ferrandiz, 2009; Korchagina, Millier, Toumi, Vataire, & Falissard, 2016)

Price should be informed by price-value precedents for other specialist medicines	Prices are usually considered relative to other treatments in same disease area. In OMPs, it appears likely that informal price comparisons are undertaken.	Mostly	(AIFA, 2016; Folino-Gallo et al., 2008; Tordrup, Tzouma, & Kanavos, 2014)
Beyond product value, price and reimbursement status should be modulated to reflect other considerations, such as societal preferences, rarity, budget impact and sustainability of innovation in rare diseases (See Table 2)	Budget impact is a key consideration. No explicit process for incorporating societal preferences or sustainability of innovation in rare diseases.	Somewhat	(Jorgensen & Kefalas, 2015)
If cost-effectiveness is applied, ICER thresholds should be modulated to reflect specificities of rare diseases	CE analyses play a supplementary role in Italy (only a few regions: Veneto, Emilia Romagna and Tuscany use it as a decision-making variable), there are no formal ICER thresholds in place. Treatments that are cost-effective may be restricted or denied reimbursement due to budget concerns.	Somewhat	(Jorgensen & Kefalas, 2015)
Balances incentives for new research investment in rare diseases while maximising value for money for healthcare systems	Different initiatives have been established to improve access to ODs and balance incentive: (a) 648/96 Law, (b) compassionate use, (b) off-label use and (d) Fondo AIFA 5%. In particular, half of the “Fondo AIFA 5%” is devoted to providing access to medicines for rare diseases awaiting marketing authorisation.	Mostly	(AIFA; AIFA; AIFA; INTEXO, 2016; Tordrup et al., 2014)
Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities			
Assessment builds on the decisions and recommendations at a European level	HTA is conducted by AIFA and performed on 3 levels: central, regional, and local levels. At the local level, the hospital-based HTA activity is probably the most important peculiarity of the country and the real driver of the HTA movement.	Not closely	(AIFA, 2016)
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals’ and patients’ perspectives			
Disease-specific expert physicians should be involved in the value assessment and provide direct input	Processes and strategies for the involvement of stakeholders in various phases of the HTA cycle have been implemented only in 5 of the 11 Regions in which HTA is regulated (Emilia-Romagna, Liguria, Lombardia, Puglia, and Veneto). Elsewhere, stakeholder involvement is not formalized.	Somewhat	

Patients and their carers should be involved in the value assessment in the following ways: - Systematic representation of patient associations in meetings that assess and appraise OMPs - Disease-specific patient representatives should be involved throughout the process and given appropriate training and support to contribute fully	Little formal involvement of patients in AIFA assessments. Some regional HTA programmes involve patients.	Not closely	(SIHTA, 2016)
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.			
Payers should consider uncertainty in light of disease prevalence, disease severity and unmet need, amount of prior research conducted in the disease, extent to which the manufacturer has taken reasonable steps to minimise uncertainty.	Flexible criteria regarding clinical data requirements and pricing regulations are frequently applied to ODs - higher level of clinical uncertainty and higher prices may be acceptable.	Mostly	(T. Gammie, Lu, & Babar, 2015; Morel et al., 2013)
Value assessment processes should be adaptive and continuous	Real-world evidence is collected through registries and is often a requirement for the market access of innovative therapies (specially in oncology) - P&R conditions are revised according to the outcomes generated. In addition, orphan medicines are eligible for an accelerated review process – the pricing and reimbursement decision must take no more than 100 days (Law 98/2013; 90–100 days vs 180 for non orphans).	Mostly	(Jorgensen & Kefalas, 2015) ADD REF
P&R decisions should allow movement both up and down with newly generated evidence on value	The P&R contracts/conditions are negotiated for a period of two years. However, all price movements have been negative - there is no evidence of a price increase.	Mostly	(Garau & Mestre-Ferrandiz, 2009; Morel et al., 2013)
Where adaptive processes are required, all parties (payers, HTA agencies, involved HCP, patients and industry) need to agree on this iterative process	In Italy, during drug registration, AIFA and companies negotiate an agreement that is valid for 2 years (most of the cases). A process for real-world data collection (mostly based on registries) is put in place. The parties meet again after 2 years if new evidence is available and a new agreement is negotiated based on the new data.	Mostly	(Morel et al., 2013)

Where possible, the collection and analysis of real-world data should be co-ordinated at a European or international level and should be integrated in disease level registries and databases	Registries are national and are not shared with other European countries. Most OMPs are covered by the national monitoring registry: *Registro Nazionale Farmaci Orfani.*	Not closely	(AIFA; Jommi & Minghetti, 2015)
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations			
Wherever possible, reimbursement decisions should seek to ensure that all patients specified in the product license should receive access to treatment	Regional authorities contribute to inequity in access especially for 'expensive drugs'. AIFA may apply 'Restricting notes for prescription' whereby it restricts reimbursement to specific patient populations, or 'Therapeutic plans' that conditions reimbursement to the drug prescription by specialised health care centres.	Somewhat	(Garau & Mestre-Ferrandiz, 2009; Morel et al., 2013)
Reimbursement may be reflective of situations where there is a broad spectrum of disease and clearly defined patient subgroups in which OMP value substantially differs		Somewhat	(Morel et al., 2013)
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs			
Funding for OMPs should be co-ordinated at a national level in order to avoid disparities in access between regions	The final price, funding and adoption decisions lie with each of the autonomous 21 regions, which at times results in significant differences across regions mostly due to budget constraints and public health strategies. However, a reimbursement ceiling price is set at national level, and, if the product is granted 'innovative classification' by AIFA, it must be made available in all regions.	Somewhat	(Jorgensen & Kefalas, 2015)
It is preferable that funding for OMPs should come out of normal healthcare budgets rather than from ear-marked rare disease funds that do not allow for a long-term perspective	OMPs are funded out of national budgets once they are assessed and recommended by AIFA. While the conclusion is reached, Fondo AIFA 5% is used fund to patient access to OMPs.	Mostly	(AIFA; Garau & Mestre-Ferrandiz, 2009)
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability			
Manufacturers, payers and HTA agencies should collaborate nationally to improve forecasting of expenditure and ensure adequate funding of OMPs	There is no clear collaboration amongst all stakeholders for forecasting OMPs expenditure.	Not closely	

Early stage dialogues amongst all stakeholders should be put in place to ensure the long-term sustainability of outcomes	AIFA does not allocate sufficient time to early stage dialogue processes at the moment.	Not closely	
Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level			
Collaborate with other European payers in regards to value assessment and data generation	Italy is a participating member State of the EUnetHTA Joint Action 3 which aims to define and implement a sustainable model for the scientific and technical cooperation on HTA. It is not clear if this influences individual product decisions.	Somewhat	(EUnetHTA, 2016)

5.5 Spain

Sub-Principle	Comment	Alignment	References
Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework			
Decision-makers should consider OMP value from the perspective of patients, the healthcare system and wider society	They apply the same criteria as for other medicines. Also consider the severity of the disease, the specific needs certain subgroups, therapeutic and social value, existence of alternative treatments, the degree of innovation and rationalization of health spending.	Somewhat	(Mestre-Ferrandiz, Puig-Peiro, & Towse, 2010)
Core elements of value and other considerations (See Table 2 below)		Somewhat	(Mestre-Ferrandiz et al., 2010)
Societal values underpinning value assessment are explicit?	No explicit reference to what kind of societal values would be considered.	Not closely	(Expert feedback)
Use of multi-criteria decision analytic (MCDA) frameworks approach?	Pilot study - development of MCDA framework (EVIDEM) for healthcare decision-making in Catalonia: EVIDEM framework was considered a useful tool to complement the current CatSalut evaluation methods; however, it is not implemented yet.	Somewhat	(Gilabert-Perramon et al., 2016; Sussex et al., 2013)
Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value for money and adjusted to reflect other considerations beyond product value			
Reimbursement decisions should be based on product value	Drug expenditure is the driving force for decision making regarding reimbursement however, factors like degree of innovation, severity and consequences of Rare Diseases are also considered.	Somewhat	(Insights in Life Series, 2015)

Price should be informed by price-value precedents for other specialist medicines	Increase emphasis on comparing that the prices of new drugs are aligned with existing therapeutic options. International benchmarking and therapeutic referencing.	Mostly	(WHO, 2013b)
Beyond product value, price and reimbursement status should be modulated to reflect other considerations, such as societal preferences, rarity, budget impact and sustainability of innovation in rare diseases (See Table 2)	Budget impact is a key consideration. No explicit process for incorporating societal preferences or sustainability of innovation in rare diseases.	Somewhat	(Jorgensen & Kefalas, 2015)
If cost-effectiveness is applied, ICER thresholds should be modulated to reflect specificities of rare diseases	Spain does not use formal cost-effectiveness analysis. Although the submission of a CE analysis by the manufacturer is compulsory for the national assessment, its P&R impact is limited; strict budget constraints dictate a highly cost-sensitive pricing environment, where budget impact is the key driver of negotiations at all levels.	N/A	(CRITERIOS DE FINANCIACIÓN Y REEMBOLSO DE LOS MEDICAMENTOS HUÉRFANOS; Jorgensen & Kefalas, 2015)
Balances incentives for new research investment in rare diseases while maximising value for money for healthcare systems	Long P&R processes in Spain (about 2 years or more for regional assessment) causes lower accessibility to drugs compared to other countries in the EU. However, early access regulations are in place and drugs cost are still covered by the national system even if the P&R process is not finished. There is also a regulation that authorizes importation from other EU countries while products are being assessed by the Ministry of Health.	Somewhat	(Expert feedback)
Principle 3: All official regulatory and health technology assessments of OMPs undertaken at the European level should be acknowledged by national health authorities			
Assessment builds on the decisions and recommendations at a European level	Overall assessments done by national and regional agencies are similar to EPAR reports. However, in recent times, the national authorities have been openly challenging the applications not because of the efficacy or evidence received but because of the high prices for OMPs: 12-13 drugs have been rejected which were approved by the EMA.	Somewhat	(Expert feedback)
Principle 4: The assessment and appraisal of OMPs in Europe should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives			

Disease-specific expert physicians should be involved in the value assessment and provide direct input	In Catalonia, different stakeholders such as the patients, carers, physicians and geneticist participate in the committee meeting to discuss positioning of the drug (do not discuss price). Some regions are trying to integrate patient's opinions in different ways. However, at the national level formal patient involvement in drug assessment is hugely restricted. Decisions on reimbursement status and price negotiations are most often conducted by committees composed of representatives from Ministry of Health and Inter-Ministerial Pricing Committee.	Somewhat	
Patients and their carers should be involved in the value assessment in the following ways: - Systematic representation of patient associations in meetings that assess and appraise OMPs - Disease-specific patient representatives should be involved throughout the process and given appropriate training and support to contribute fully		Somewhat	(WHO, 2013b)
Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.			
Payers should consider uncertainty in light of disease prevalence, disease severity and unmet need, amount of prior research conducted in the disease, extent to which the manufacturer has taken reasonable steps to minimise uncertainty.	Orphan medicines follow the same P&R process as any other drug entering the Spanish market.	Somewhat	(Expert feedback)
Value assessment processes should be adaptive and continuous	In some regions such as Catalonia, there is a process in place where hospitals and patient registries will collect data on the usage of the innovative therapies. After reviewing the evidence, the regional body updates its reimbursement decision and expands or limits usage of the drug.	Somewhat	(Expert feedback)
P&R decisions should allow movement both up and down with newly generated evidence on value	Ministry of Health gives initial price for an OMPs which is then revised systematically by regional agencies. In case of indication expansion either the new indication is rejected or treatment price is further discounted at regional levels to mitigate increase in the patient numbers.	Somewhat	(Expert feedback)
Where adaptive processes are required, all parties (payers, HTA agencies, involved HCP, patients and industry) need to agree on this iterative process	Managed entry agreements, payment-by-results are systematically used at regional levels.	Mostly	(Tolley & Palazzolo, 2014)

Where possible, the collection and analysis of real-world data should be co-ordinated at a European or international level and should be integrated in disease level registries and databases	Population register is a general, anonymized national register and not specific to drugs. There are specific therapeutic registries, managed at national or regional level. There can be differences between registries across regions to an extent that a region can ban registries which are controlled at national level. The Spanish Rare Diseases Registries Research Network (SpainRDR) is a project aimed to build the National Rare Diseases Registry in Spain based on the input of two different methods: patient outcome research registries and population-based registries.	Not closely	(de la Paz et al., 2014; Payer expert feedback)
Principle 6: All eligible patients within the authorised label of an OMP should be considered in the reimbursement appraisal although different decisions on access may apply to different sub-populations			
Wherever possible, reimbursement decisions should seek to ensure that all patients specified in the product license should receive access to treatment	Normally ODs are administered in inpatient settings and are, therefore, reimbursed 100%.	Mostly	(Tordrup et al., 2014)
Reimbursement may be reflective of situations where there is a broad spectrum of disease and clearly defined patient subgroups in which OMP value substantially differs	Regional agencies are stricter than national body in defining patient sub-groups. Therefore, they usually require evidence to have a detailed understanding of how certain patient sub-groups respond to the treatment to influence reimbursement decision at the regional level.	Somewhat	
Principle 7: Funding should be provided at the national level to ensure patient access to OMPs			
Funding for OMPs should be co-ordinated at a national level in order to avoid disparities in access between regions	Maximum price is decided at the national level and regions have obligations to fund them, however, regions like Catalonia, Andalusia, will negotiate the prices below the national agreed price. Hospitals' pharmacy and therapeutic commissions autonomously decide on discounts and volume based on patient numbers. Payment methods vary by regions.	Not closely	(Young, Soussi, Hemels, & Toumi, 2017)
It is preferable that funding for OMPs should come out of normal healthcare budgets rather than from ear-marked rare disease funds that do not allow for a long-term perspective	There is no provision of a special budget for OMP.	Mostly	(Expert feedback)
Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability			
Manufacturers, payers and HTA agencies should collaborate nationally to improve forecasting of expenditure and ensure adequate funding of OMPs	Regions use informal process to estimate forecasting by inviting patients, companies and industry association.	Somewhat	(Payer expert feedback)

Early stage dialog between all stakeholders should be put in place to ensure long term sustainability of outcomes	Company initiated early dialogue with the reimbursement agency as soon as the CHMP opinion is positive, but this is an informal process mainly.	Somewhat	(Payer expert feedback)
Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level			
Collaborate with other European payers in regard to value assessment and data generation	Yes - among the lead partners of the EUnetHTA Joint Action 3 but it is unclear to what extent this has impact on local decisions.	Somewhat	(EUnetHTA, 2016)

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