PhRMA

PhRMA HTA Seminar: Towards the Trial Introduction of HTA in Japan from 2016 Latest trends to consider

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Credentials and disclaimer

David Grainger

- Over 35 years experience in pharmaceutical industry in New Zealand, Australia, Europe and the US
- Full member of Board of Directors, Health Technology Assessment International (HTAi)
- Chair of PhRMA International HTA Task Force
- Former member of the *Access to Medicines Working Group*, a high level industry and government medicines policy group appointed by the Australian Minister of Health
- During the past four years has undertaken short term assignments in Brussels and London, working with industry groups in both locations on evolving HTA processes

Disclaimer

Views expressed do not necessarily represent those of Eli Lilly and Company nor the entire pharmaceutical industry

PhRMA's position on HTA context

1 What is HTA?

- Health Technology Assessment (HTA) is an approach to assess the value of various treatment options from a holistic perspective including scientific, economic and societal/ ethical aspects so as to enable well-informed decisions to deliver the best possible results for all patients
- It should also be used in such a way as to promote innovation in patients' medical treatment options and ultimately achieve a higher quality health care system

2 HTA in Japan and opportunity for further enhancement

- In Japan, HTA has already been incorporated over many years under the current reimbursement and pricing systems without negative impacts on patients' access
- Specifically, the system is designed to assess the value of treatment options based on efficacy and safety as well as a broad set of criteria including societal and ethical aspects
- While the system already exists, there is still an opportunity for further enhancement in order to appropriately assess treatment options and rewarding innovation

3 Learning from HTA in other countries

- HTA has been conducted and evolved in various countries under different healthcare systems and issues encountered. No single country, however, has been identified as having the best practice with each country facing some downside:
  - Delaying or limiting patients' access to innovative treatment options
  - Discouraging innovation
- We need to learn from those challenges in enhancing HTA in Japan

Source: PhRMA

1 HTA is any approach to assess value of various treatment options from holistic perspective

HTA is an assessment of value of all 3 categories of treatment options…

- Drugs
- Devices
- Medical procedures
  - Diagnostics, operations etc.

…with broader criteria than those required for approval…

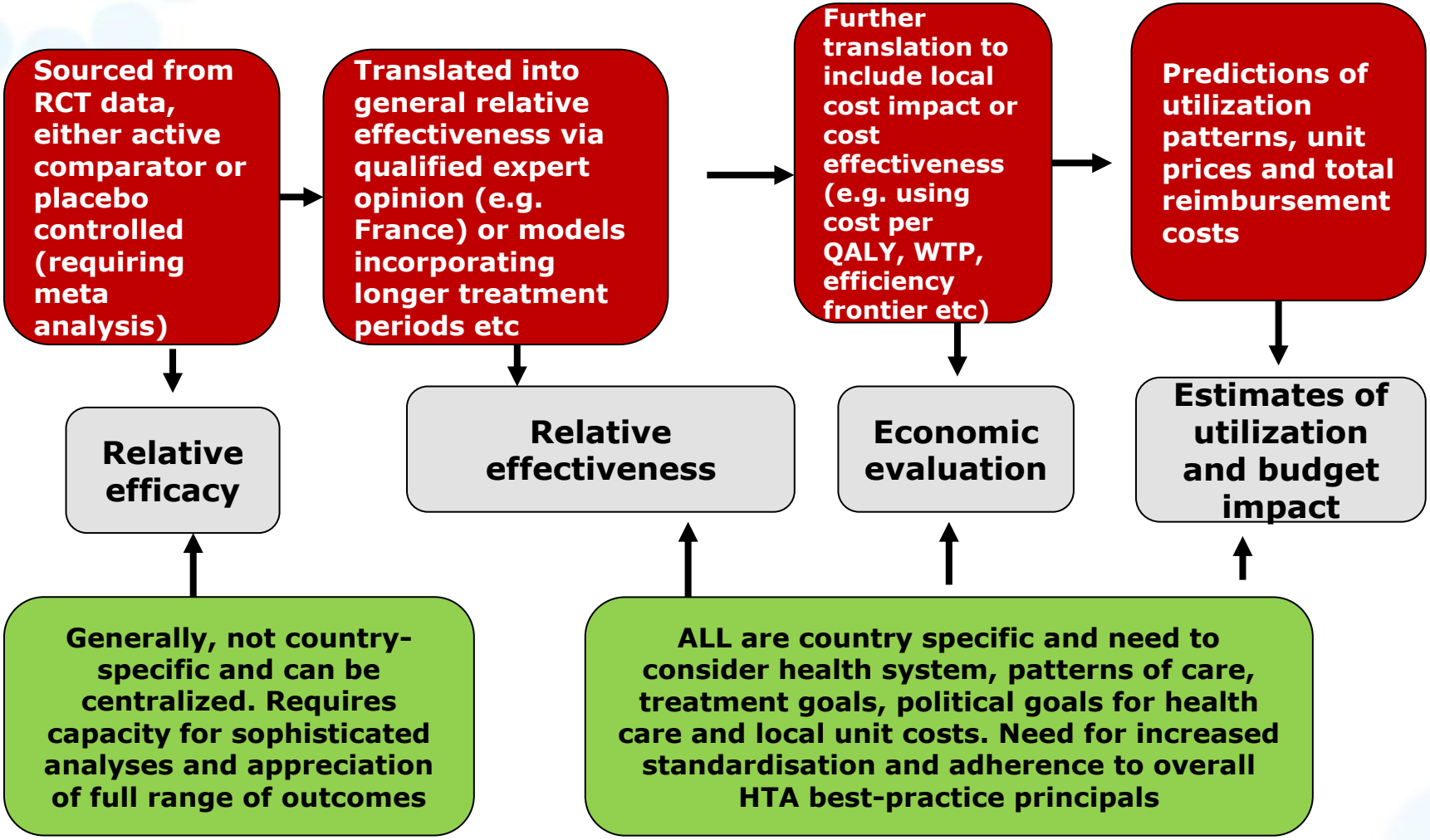
- Relative efficacy
  - Efficacy and safety from clinical trials
- \+
- Society and ethics
- Economics (HEE[1])
- Clinical effectiveness in real world
- Epidemiology

… to bring benefits to all the society

- Well-informed decisions by physicians /patients
- Higher quality healthcare services
- Promotion of innovation

1. HEE (Health Economic Evaluation) is a narrower sense of value assessment which focuses only on economics (benefit/cost)
Source: PhRMA

1 HTA building blocks... *Concept is great but a lot to do*



2 In Japan, HTA has already been incorporated under the gov't reimbursement and pricing systems

	Drug / device	Medical procedures
Approval	<Criteria> • Efficacy and safety <Assessed by> • PMDA[1)]	No approval process
Reimburse-ment	Essentially almost all the approved drugs/devices are reimbursed	<Criteria> • Efficacy and safety incl. societal and ethical needs <Assessed by> • Sub-committee on Medical Procedure Assessment[3)]
Pricing	<Criteria> • Efficacy and safety <Assessed by> • DPO(drugs)/IMMO(devices)	<Criteria> • Efficacy and safety as well as social benefits <Assessed and decided by> • Chuikyo
How HTA incorpo-rated	Efficacy/Safety assessed and reflected in pricing decision • Base price and premium	Efficacy/Safety and social benefits assessed and reflected in reimbursement/ pricing decision

1.Drug Pricing Org., 薬価算定組織; 2. Insurance and Medical Material Org., 保険医療材料専門組織; 3. 医療技術評価分科会
Source: MHLW

3 Reasons for centralized HTA introduced in other countries does not apply to Japan

Background of HTA enhancement

	Outside of Japan		Japan
Pricing system	**Free** pricing[1] 	⟷	Price **controlled** by government
Overall HC cost	HC expenditure growth **outpaced** GDP 	⟷	HC expenditure growth at **similar level** to GDP
Regional disparity	Significant **regional disparity**[2] 	⟷	**Universal** reimbursement and pricing

1. Manufacturers/providers to set price freely based on negotiation with the authority or hospitals; 2. Disparity in reimbursement and price of treatment options among region
Note: Separate Fact pack contains more detailed information about HTA in UK, Sweden, Germany, France, Australia and South Korea including background of HTA introduction

3 Each country facing downside around patients' access to innovative treatment options

Major downside associated with HTA		Countries with some experience of downside
Outcomes	Absolute/timely access to innovative new technologies for patients limited/delayed	
Underlying reasons	a. Assessment is not based on broad criteria to capture innovativeness	
	b. Assessment is based on a narrow view of the evidence and may reject non-RCT inputs	
	c. HTA process taking long time	

HTA is still evolving in each country to address issues

Note: Example of each "side effect" is in the appendix

Four basic policies and principles establish a framework to enhance current HTA in japan

Basic policies	Guiding principles
1 **Patients' access** to various treatment options should be maintained at the current level	1a **Ensure reimbursement allows all eligible patients to access the product**
	1b **Maintain prompt reimbursement after regulatory approval**
2 **Appropriate assessment** of holistic value of treatment options should be conducted	2a **Consider the broad effects of treatment options more explicitly**
	2b **Use the most appropriate methodology and criteria for evaluation**
	2c **Establish relevant databases and expertise for adequate assessment**
	2d **Ensure transparency in the methodologies, processes and results**
3 **Burden** associated with value assessment should be minimized	3a **Minimize incremental burden for data collection**
	3b **Minimize the administrative cost and bureaucracy of the assessment**
4 **Innovation** should be rewarded sufficiently by adequate assessment	4a **Reward innovation appropriately based on the assessment**

Note: The Guiding Principles have been developed based on key findings of HTA in and outside of Japan. Also international research works on HTA have been referred to in the process, including *"Key principles for the improved conduct of health technology assessments for resource allocation decisions"* by Drummond et al (2008)

Guiding principle 1b: Maintain prompt reimbursement after regulatory approval

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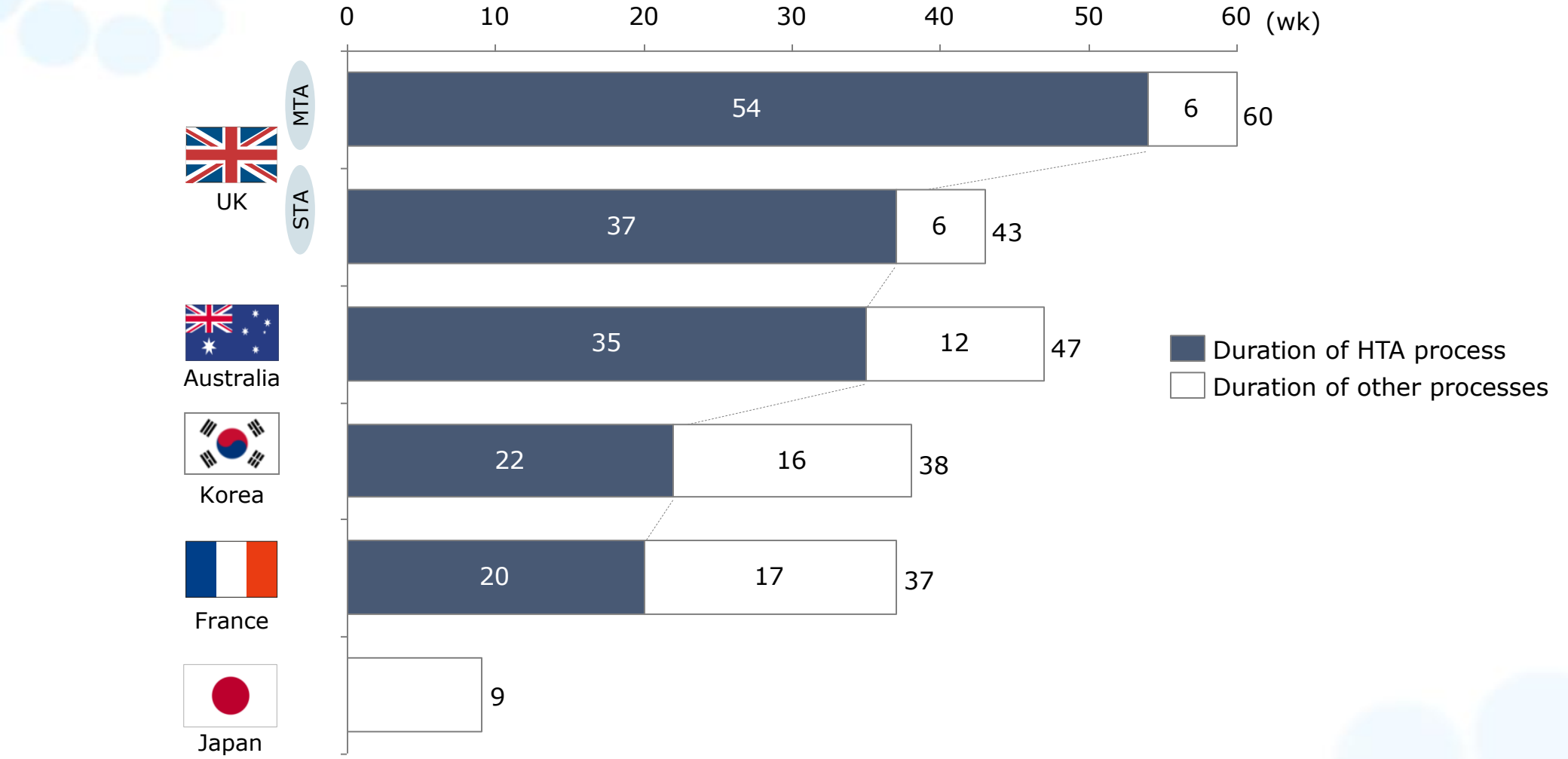
1b

HTA delays patients' access if applied at approval

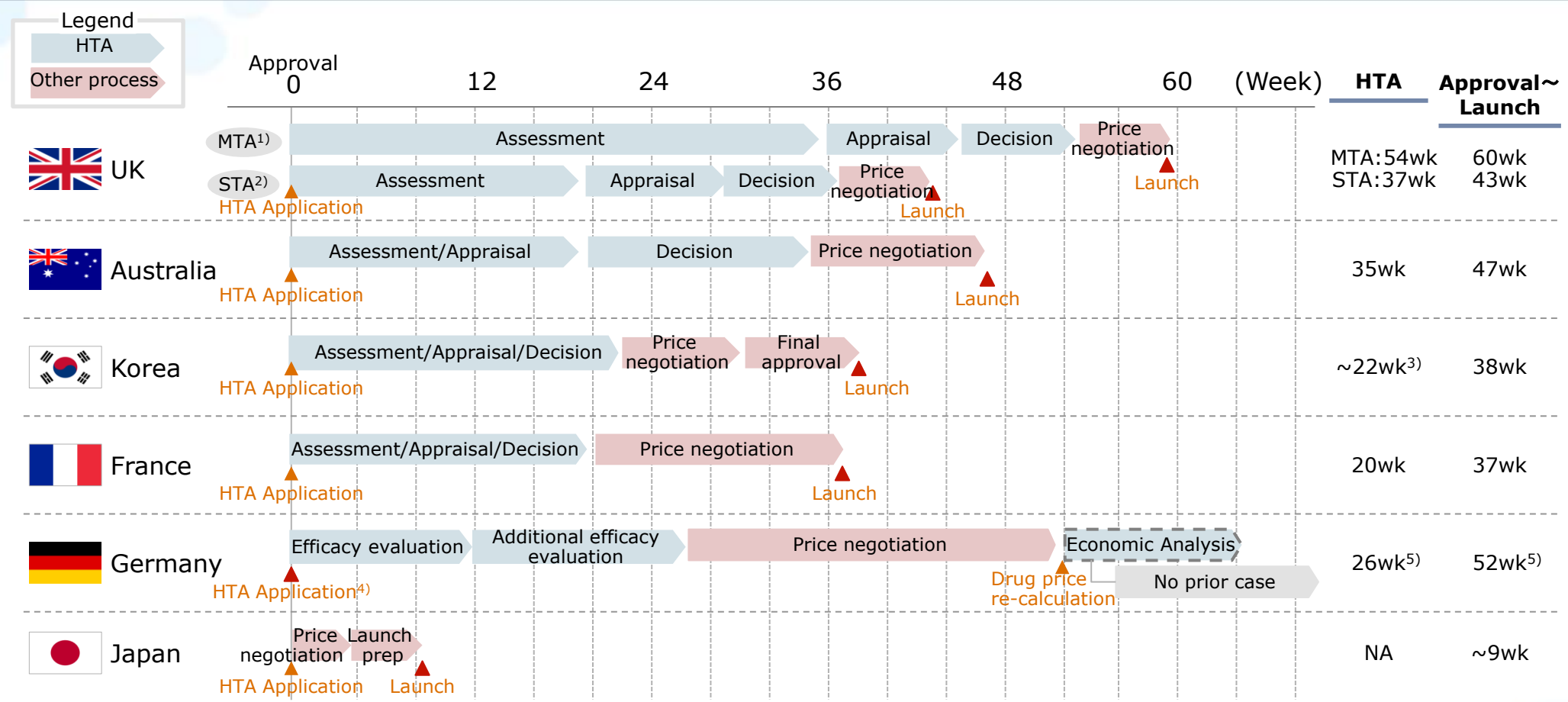
Duration of drug approval to launch across countries



Source: NICE; HAS; PBAC; HIRA; Expert interview

1b In countries which are introducing HTA, time horizon from approval to launch is longer

Process and timeline from approval to launch



Actual time horizon from approval to launch may be longer than publicly disclosed timeframes

1. MTA – Multiple Technology Appraisal; 2. STA – Single Technology Appraisal; 3. Total of HTA and reimbursement term 4. Showing the process of when efficacy proved for drugs (When efficacy isn't proved, reference pricing will be applied without price negotiation); 5. Economic analysis time is not included because no prior case
Source: BCG analysis

Guiding principle 2a: Consider the broad effects of treatment options more explicitly

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2a

Need to consider both direct/indirect cost & benefits

Direct and indirect costs and benefits to be assessed in HTA

	Cost	Benefit
Direct	**Costs of health technologies**	**Clinical outcomes**
	Operating expenditures • Wages, Rents, Utilities etc	**Savings in medical / health related costs**
	Others • Fees, Subsidies, Interest, Donations etc	**Behavioral and functional outcomes**
		Quality of life
Indirect	**Productivity losses** • Work absence, Labor costs	**Savings in social care, benefits in return to work and associated productivity gains**
	Time costs • Travel, Waiting, etc	
	Others • Storage, Packaging, Distribution, Wastage etc	

Source: U.S. National Information Center on Health Services Research and Health Care Technology (NICHSR)

Guiding principle 2b: Use the most appropriate methodology and criteria for evaluation

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2b UK and other countries facing criticism on the single use of QALY

Methods and issues surrounding cost effectiveness analysis

Methods of cost-effectiveness analysis

	Effectiveness	Threshold
UK	**QALY** use is required	**20,000-30,000 £/QALY (3.6-5.4M yen[1])**
France	**QALY** is not always required • Only for drugs that meet criteria/ required following period of reimbursement	**None**
Sweden	**QALY** use is recommended	**40,000 SEK/QALY (5.6M yen [2])** • Performance-based
Australia	**QALY** use is recommended	**40,000 $/QALY (3.7M yen[3])** • Target range (rather than a specific and enforced threshold)

Issues surrounding cost effectiveness analysis

No universal approach to calculating QALYs

- "Calculating QALYs is complicated and depending on the perspective used to elicit preferences, results can change"
  - Dr. Kamae, Tokyo University School of Public Health

Limitations of measurement under single QALY

- "You cannot account for the societal benefit of a new drug by just looking at QALYs"
  - Praveen Thokala, University of Sheffield, Health Economics Professor
- "QALY does not accurately capture patient values"
  - Michael Drummond, York University, Health Economics Professor, Director of Center for Health Economics

There is no consensus for eliciting patient preferences into calculating QALYs

- "There is lack of agreement even among researchers which can prevent simple comparisons"
  - UK HTA Consulting Group, CEO

1. 179JPY/GBP; 2. 13.91JPY/SWK; 3. 91.87JPY/AUD

Source: Kamae (2012) 43(8), 668-692;Decision making in Health and Medicine (2011);NICE; HAS; TLV; PBAC

1a France: 26 drugs have been included for HTA evaluation of which only 4 have published results

Drugs evaluated by HTA in France

Drugs assessed during HTA			Results[1)]
Brand name	Generic name	Therapeutic use	✓: Published decisions
Adempas	Riociguat	Pulmonary hypertension	✓
Tivicay	Dolutegravir	HIV	✓
Sovaldi	Sofosbuvir	Hepatitis C	✓
Kadcyla	Trastuzumabemtansine	Breast cancer	✓
Entyvio	Vedolizumab	Ulcerative colitis, Chron's disease	--
Romiplate	Romiplostim	Idiopathic thrombocytopenic purpura	--
Botox	Botox	Botsulin therapy	--
Olysio	Simeprevir	Hepatitis C	--
Zostavax	Zoster Vaccine	Zoster	--
Xofigo	Radium 223	Prostate cancer	--
Revlimid	Renalimid	Multiple myeloma	--
Defetelio	Defibrotide	Pulmonary veno-occlusive disease	--
Lemtrada	Alemtuzumab	Multiple sclerosis	--
Vectibix	Panitumumab	Colon cancer	--
Tecfidera	Dimethyl fumurate	Multiple sclerosis	--
Rotarix	Rotavirus vaccine	Rota virus	--
Rotateq	Rotavirus vaccine	Rota virus	--
Opsumit	Macitentan	Pulmonary hypertension	--
Mitraclip	Mitraclip	Mitral valve deficiency	--
Harvoni	Lldipasvir + Sofosbuvir	Hepatitis C	--
Daklinza	Daclatasvir	Hepatitis C	--
Fluenz Tetra	influenza A & B virus strains	Influenza	--
Gazyvaro	Obinutuzumab	Chronic leukemia	--
Imbruvica	Ibrutinib	Chronic leukemia	--
Zydelig	Idelalisib	Chronic leukemia	--
Xolair	Omalizumab	Asthma	--
Esbriet	Pirfenidone	Idiopathic pulmonary fibrosis	--

1. IHS, Based on released Efficiency Opinion Reports
Source: HAS; IHS; MHLW

2b UK: Several patient access reforms have been initiated but their effects remain subpar

Policy changes surrounding HTA in the UK

UK

Initiatives		Start Date	Issues
Increase of threshold for certain drugs	**Proposal of relaxing thresholds depending on disease states** • If certain criteria are met, thresholds are allowed up to 50,000£/QALY	1/2009	**Strict criteria prevents drug access** • Access issues remain a challenge for many patients **Simply raising the threshold does not capture new technological benefits, nor wider societal benefits**
Patient Access Scheme (PAS)	**Drug manufacturers subsidize a portion of the drug cost without changing the list price**	1/2009	**Possibility of decreased market attractiveness** • Prices are set lower than at initial launch • If the drug is unable to show effectiveness, the government uses the evidence for price negotiations • As a result, pharma companies may be reluctant to launch
Cancer Drug Fund (CDF)	**Established a fund to provide access to drugs which were deemed not reimbursable through NICE** • Initiated following failed attempts through PAS • Originally proposed to end in 10/2014 but now extended through 3/2016	4/2011	**Extreme financial impact leading to difficulties maintaining fund** • "If we continue to go this path, we will run out of budget; therefore we need to manage our budget better" - UK HTA Consulting Company CEO

Source: NICE website; JPMA; Expert Interview

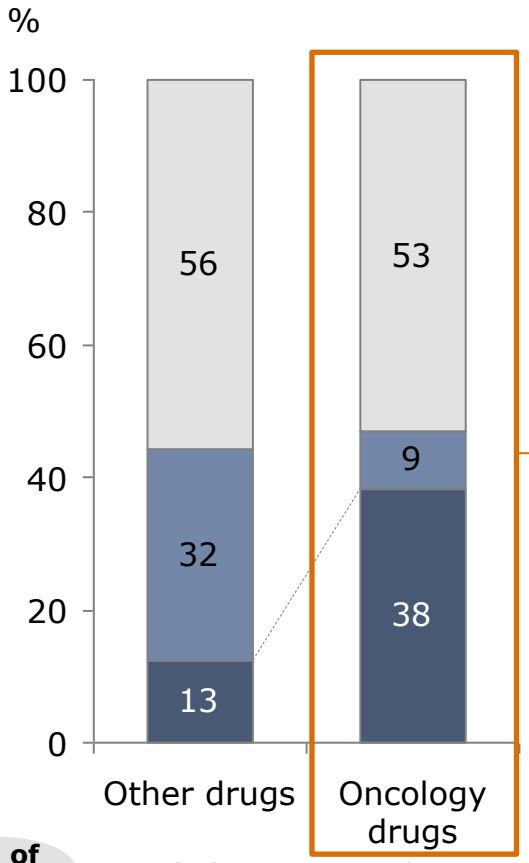
2b UK: Many oncology drugs have been denied reimbursement

Reimbursement status of UK's oncology drugs

UK

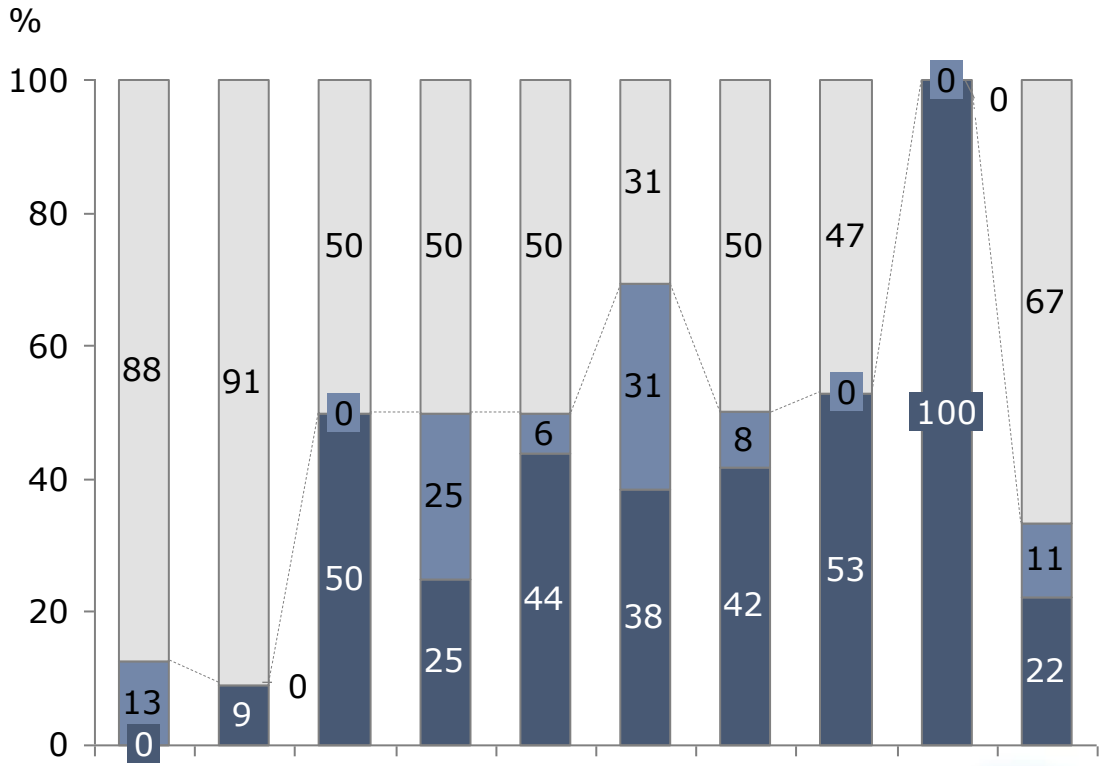
Reimbursement | Conditional reimbursement | No reimbursement

Reimbursement for oncology/non oncology[1)]



No. of appraisals	Other drugs	Oncology drugs
	248	104

Trend for reimbursement status of oncology drugs[1)]

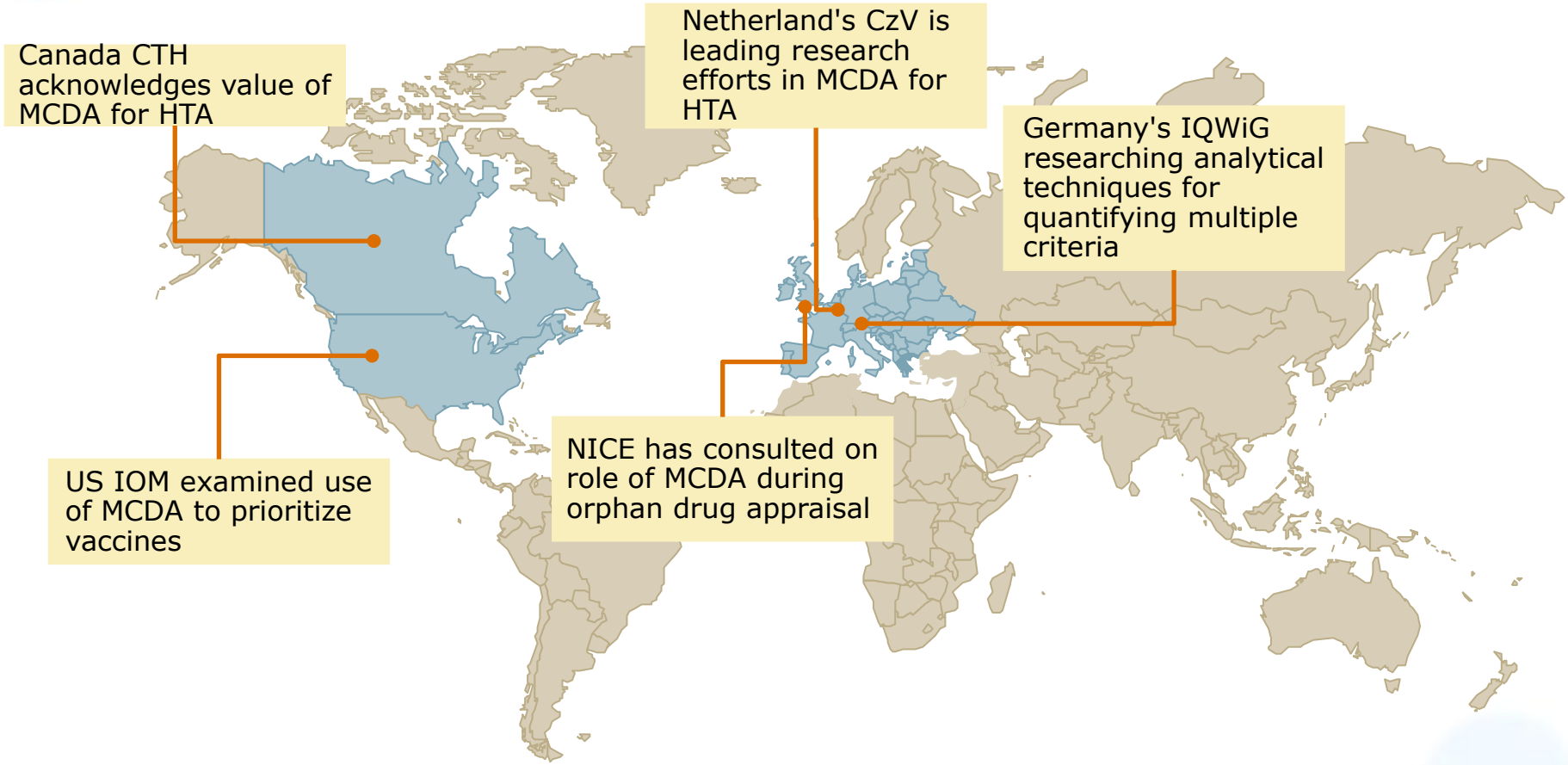


No. of appraisals	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
	8	11	8	4	16	13	12	17	6	9

1. Based on data for drugs assessed in 2005-14
Source: NICE

2b To overcome issues surrounding QALY, research using multiple criteria is underway

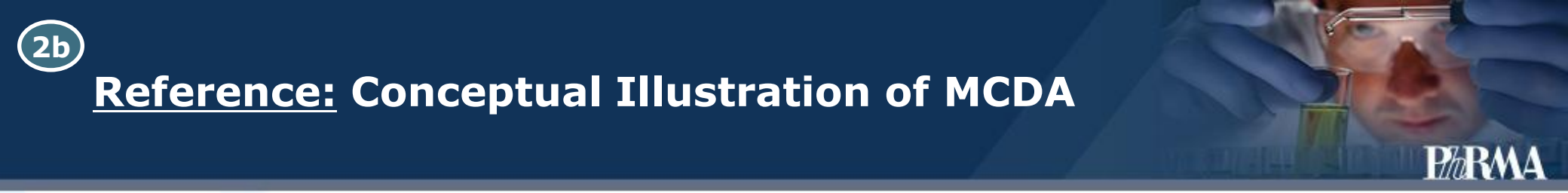
Status of multi-criteria decision analysis (MCDA) in major countries



Source: Lantis&Marsh (2014), ISPOR 19th International Meeting presentation materials

2b

Reference: Conceptual Illustration of MCDA



Criteria examined during MCDA (example)	
Financial	Cost-Effectiveness
Disease/ Drug related attributes	Disease severity
	Disease rarity
	Innovativeness of drug
	Added therapeutic value
Patient burden	Day to day activity burden
	Disease burden
	Caregiver burden
Budget related	Impact on budget

Analytical steps

1. **Select criteria for appraisal**
   - Select criteria likely to affect final decision by holding discussions with relevant stakeholders
2. **Weigh selected criteria**
   - Vary weights depending on severity/added value of criteria
3. **Calculate score based on weighted criteria**
   - Sum individually weighed criteria to be used for final decision making

2b UK: Multiple criteria considered for QALY calc.; additionally societal benefit is considered

Comparison of MCDA to conventional assessment methods

UK

	Methodology	Conventional	Multiple Criteria
Assessment	Identify the problem and alternative	✓	✓
	Define the criteria against which alternatives are compared • Selection of economic variables (hospitalization, treatment fee)	✓	✓
	• Selection of non-economic variables (disease severity, caregiver burden)		✓
Appraisal	Evaluate the ICER • Measure QALY using one parameter (QOL)	✓	
	• Use multiple criteria to elicit criteria weights for interpreting thresholds (treatment status, innovativeness of drug)		✓
	Incorporate the societal benefit perspective (equity of access, opportunity costs from disease)	✓ [1)]	✓
Decision	Arrive at a decision • Decision generated from a single measure (Cost/QALY)	✓	
	• Incorporate the societal benefit for comprehensive evaluation		✓

In addition to existing methods, incorporation of the societal perspective is underway; however use of QALY derived from multiple criteria is still underdeveloped

1. Conventional methods claim to consider societal benefit, however difficult to determine consistency

Source: Thokola et al. (2012)

2b Netherlands: Use of multiple criteria advanced and efforts to develop quantitative methods underway

Multiple criteria use in the Netherlands

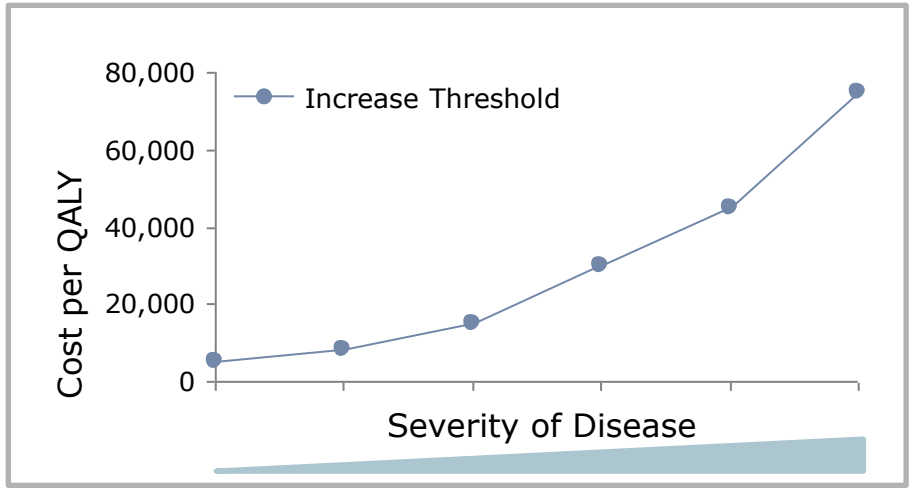
In the Netherlands, multiple criteria is already incorporated by allowing flexible thresholds

Multiple criteria during evaluations:

- Disease severity, drug necessity, therapeutic effectiveness, access, societal affordability, societal values, etc.

Instead of placing an absolute threshold, the Dutch take on the floating threshold

- Vary threshold depending on drug severity



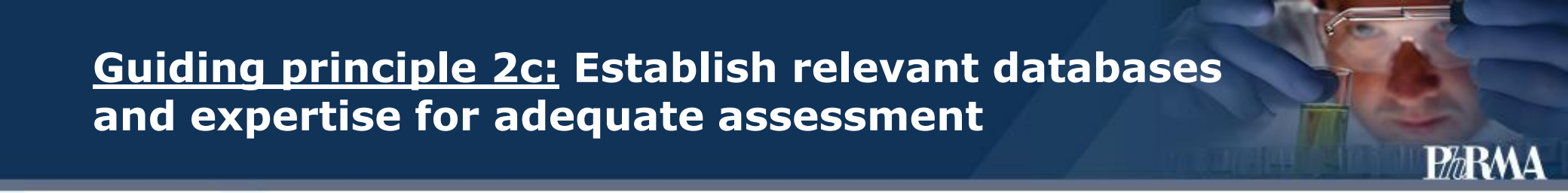
Additional efforts are in progress to establish scientific MCDA methodologies

Research around multiple criteria is underway

- Demonstrated potential use of MCDA to determine orphan drug reimbursement in international journals/conferences

Source: CzV Presentation materials (2011); Shire Report; MCDA in HTA of Orphan Drugs (2013)

Guiding principle 2c: Establish relevant databases and expertise for adequate assessment



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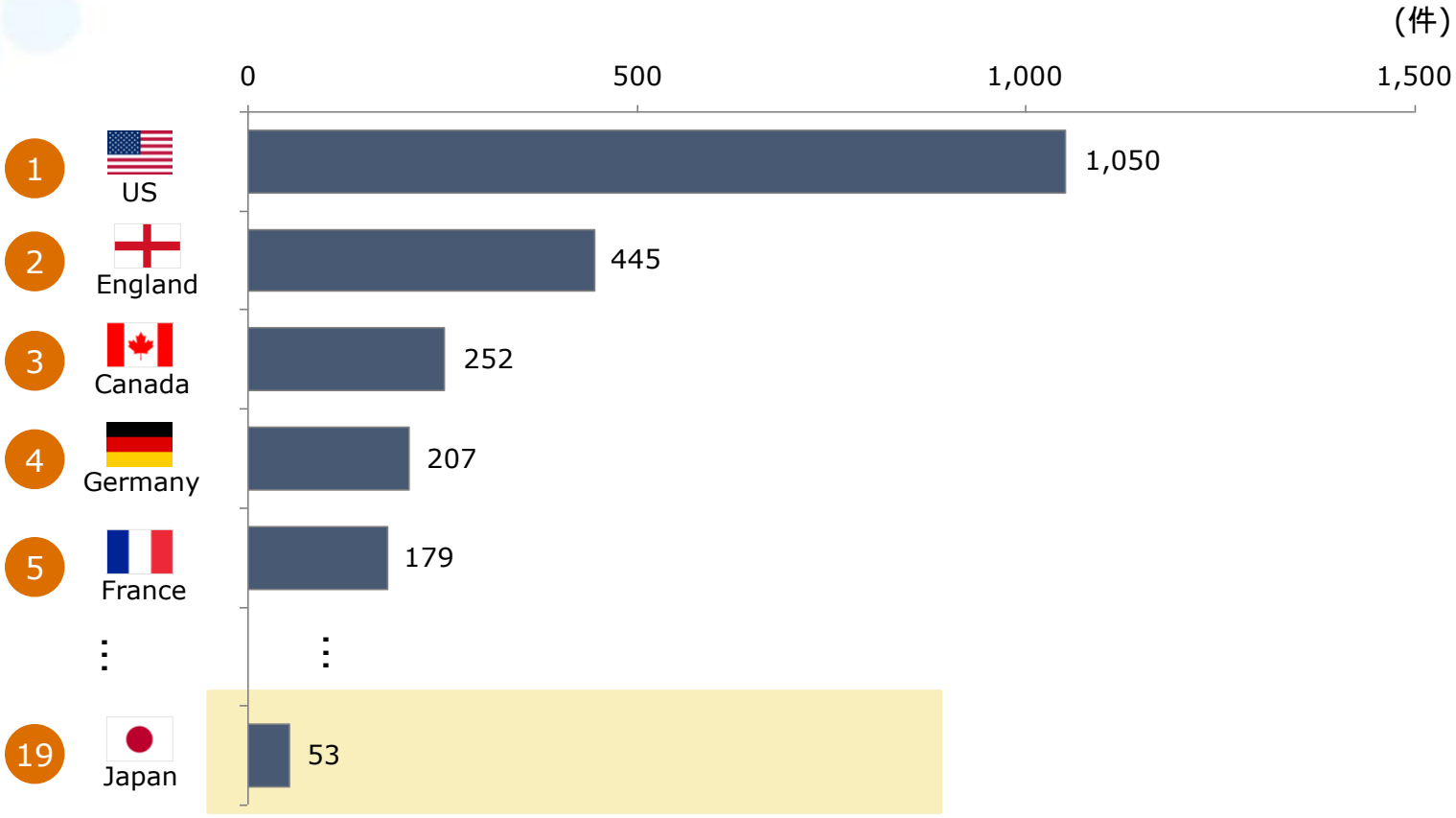
2c Japan: Use of clinical data for cost effectiveness analysis could be tough with weak basic research

Comparison of # of studies across countries

Japan



Note: Total # of studies published in top journals (Basic - Nature Medicine, Cell, J Exp Med, Clinical - New Engl J Med Lancet JAMA) in 2013-14
Source: Seisakuken news 2015

2c

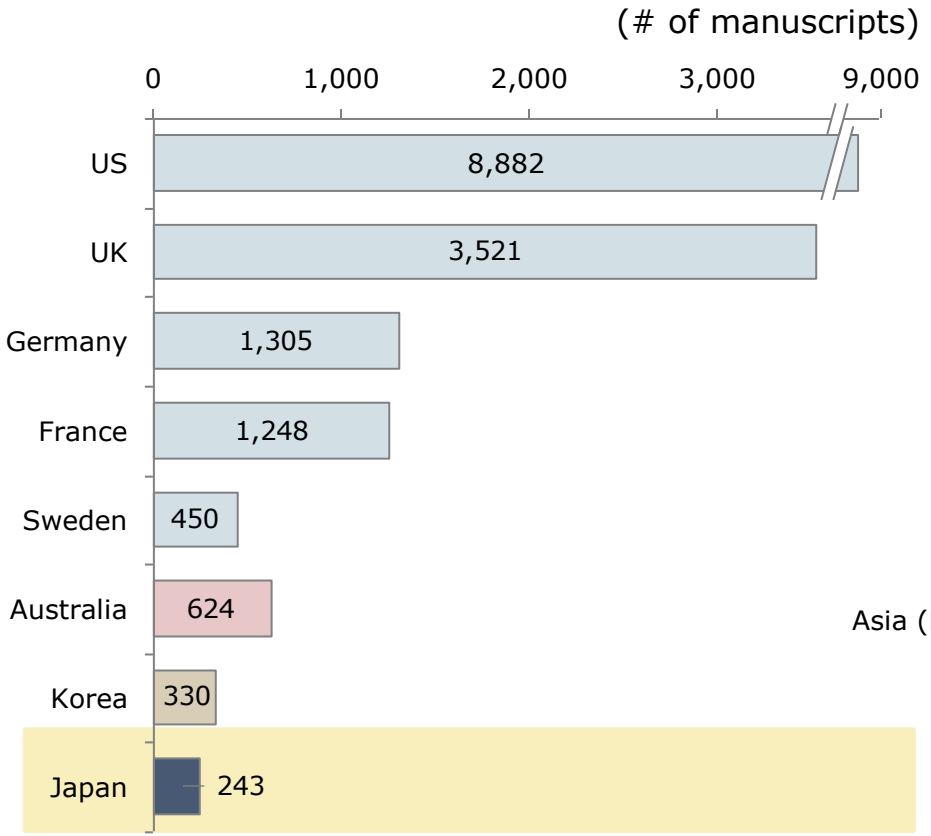
Japan lacks adequate professional expertise

Japan's infrastructure to conduct HTA

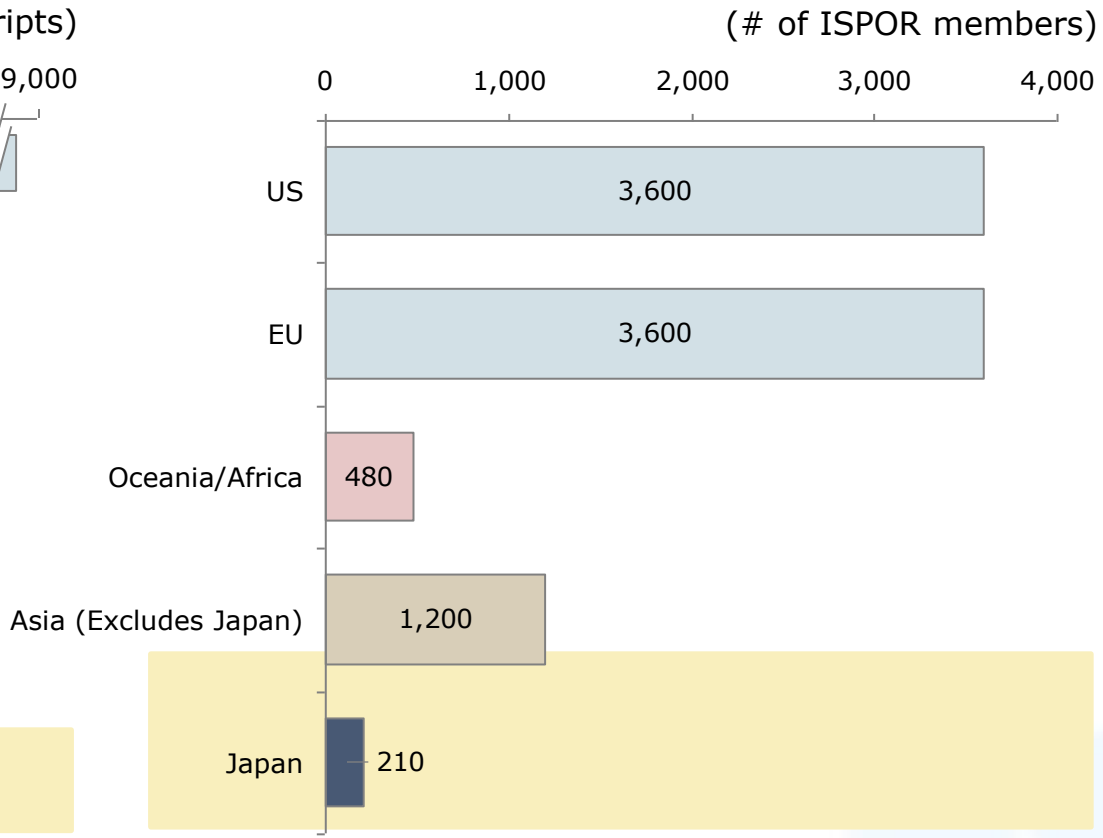
Japan

EU
Asia
Oceania/Africa
Japan

Health Economic Manuscripts[1)]



ISPOR members by Region[2)]



1. Manuscripts published in top 5 Health Economic Journals between 2009-2014；Journals include: Pharmacoeconomics, Value in Health, IJHTA, Journal of Health Economics, Health Economics; 2. Breakdown of ISPOR members by region calculated using ISPOR global count 8,700 and % of regional spread
Source: ISPOR; Web of Science

Key learnings for consideration in Japan

1. **HTA is complex! It takes time to build understanding of range of relevant outcomes, especially those relevant to patient.**

2. **Even established HTA systems are undergoing change as they try to better balance:**
   a. the need to ensure patients can access appropriate innovation
   b. the sustainability of the health system as it takes up that innovation
   c. incentives for the ongoing investment in tomorrow's innovation

3. **As well as the technical and data challenges, determining the optimal approach to decision-making is critical. While MCDA is still evolving and HTA agencies are cautious in adoption, much can be learned from the concept of multiple criteria.**

4. **It will be important to recognise BOTH the strengths of the current processes in Japan and the limited capabilities for full HTA today. By doing so, it should be possible to evolve optimal approaches for Japan that put patient outcomes first.**