Achieving market access for cell therapies: a UK perspective

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May 2014

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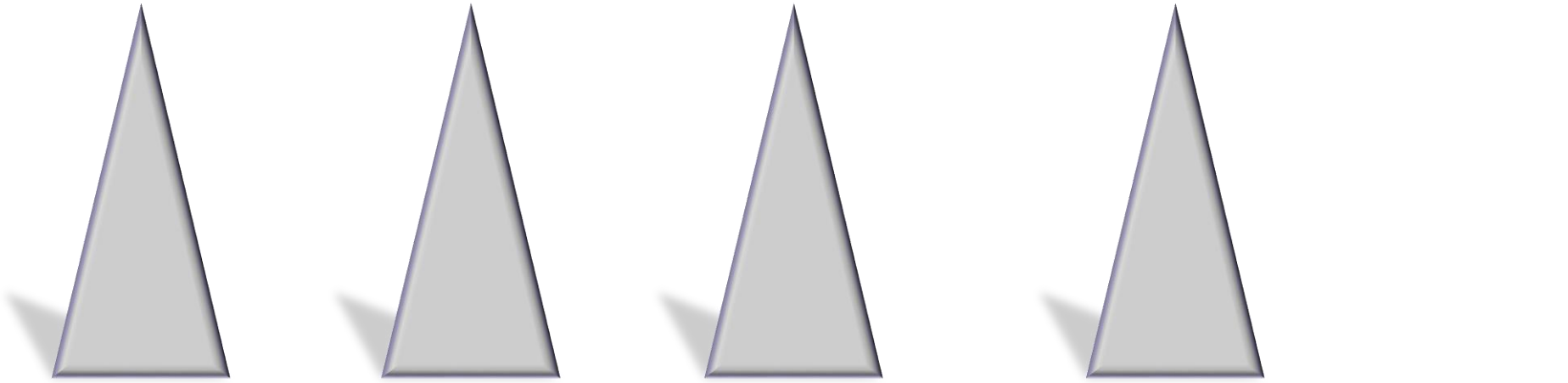
Successful commercialization depends on both regulatory approval and optimal market access



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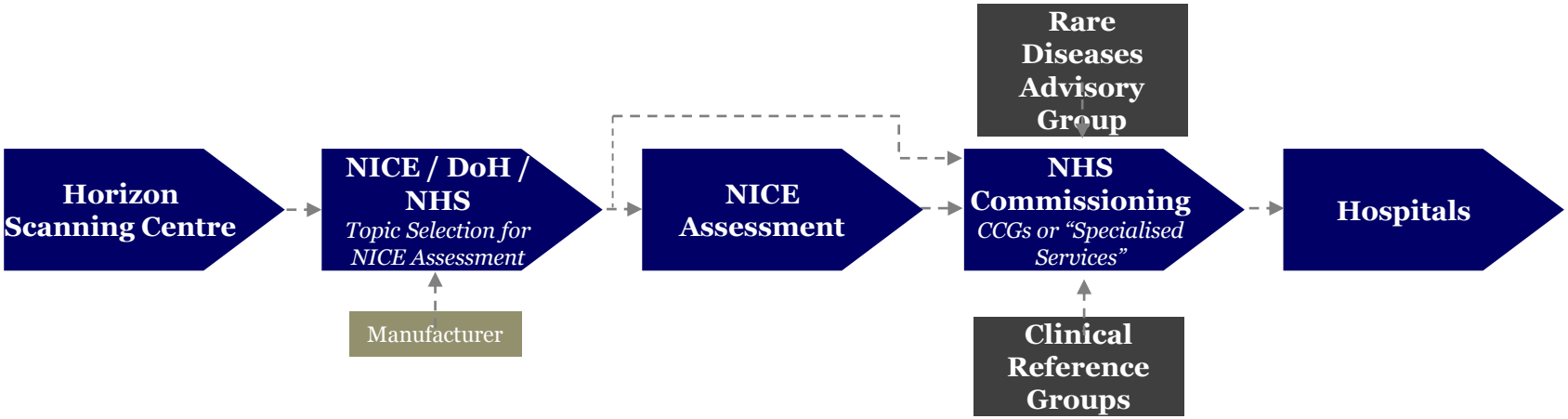
*For unlicensed therapies only, safety is the key determinant

The route to NHS adoption involves multiple stakeholders

Top-level roadmap to market access for licensed ATMPs (England*)



Cell Therapy manufacturers should engage successfully with all above stakeholders in order to maximise therapy uptake.

Equivalent to NICE assessments in Scotland are undertaken by the Scottish Medicines Consortium (SMC) and in Wales by the All Welsh Medicines Strategy Group (AWMSG); The Rare Diseases Advisory Group advices NHS England, NHS Scotland, NHS Wales, NHS Northern Ireland.

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Abbreviations: ATMP (Advanced Therapy Medicinal Product); CCGs (Clinical Commissioning Groups); NICE (National Institute for Health and Care Excellence)

Two types of NICE assessments (TA and HSTE)* result in binding obligations for NHS commissioning: TA is employed for larger target populations

Out of ~200 new products launching p.a. only ~25% are assessed by TA or HSTE

Technology appraisals (~45 assessments p.a.)

Selection criteria	Elimination criteria	Prioritisation criteria
▪ The technology is likely to result in significant: ▪ Health benefit ▪ Impact on other health-related government policies (e.g. reduction in health inequalities) ▪ NICE guidance is likely to add value because in its absence there is likely: ▪ Uncertainty over clinical and cost effectiveness ▪ Variation in the use of the technology across the country	• **Unlicensed technologies** (no plan to license) • Modification to an existing formulation or technology (e.g. me-too) • Population screening • Vaccination • HIV technology/therapy • Covered in existing guidance • Evidence lacking • Timing not close to launch • Does not address the key clinical question	• Population • The larger the target population, the greater the prioritisation • Disease severity • Including: life expectancy; how far the individual is away from perfect health; health states that incur social stigma • Resource impact • Cost of implementation, facilities, staff requirements • Claimed therapeutic benefit over available NHS treatments

TAs were originally applied to non-rare diseases, recently applied to diseases with three digit incidence.

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**Abbreviations: Technology Appraisals (TA), Highly Specialised Technologies Evaluation (HSTE)*

HSTE* is appropriate for therapies for very rare diseases; however additional criteria should be fulfilled

Selection criteria

- The target patient group for the technology **in its licensed indication is so small** that treatment will usually be **concentrated in very few centres in the NHS**
  - Originally defined as no more than 500 patients per annum
- Highly unlikely there is **a clinically meaningful alternative**
- The condition is **chronic and severely disabling**
- The technology **is likely to have a very high acquisition cost**
- The technology **has the potential for life long use**
- The target patient group is **distinct for clinical reasons** (e.g. not for genetic reasons alone)
- The technology is expected to be used exclusively in the context **of a highly specialised service**
- The **need for national commissioning is significant**
- Available data should **permit undertaking of assessment**

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*Abbreviations: Highly Specialised Technologies Evaluation (HSTE)

For licensed therapies that do not undergo TA or HSTE, other types of NICE guidance may be relevant to support adoption decisions by NHS commissioners

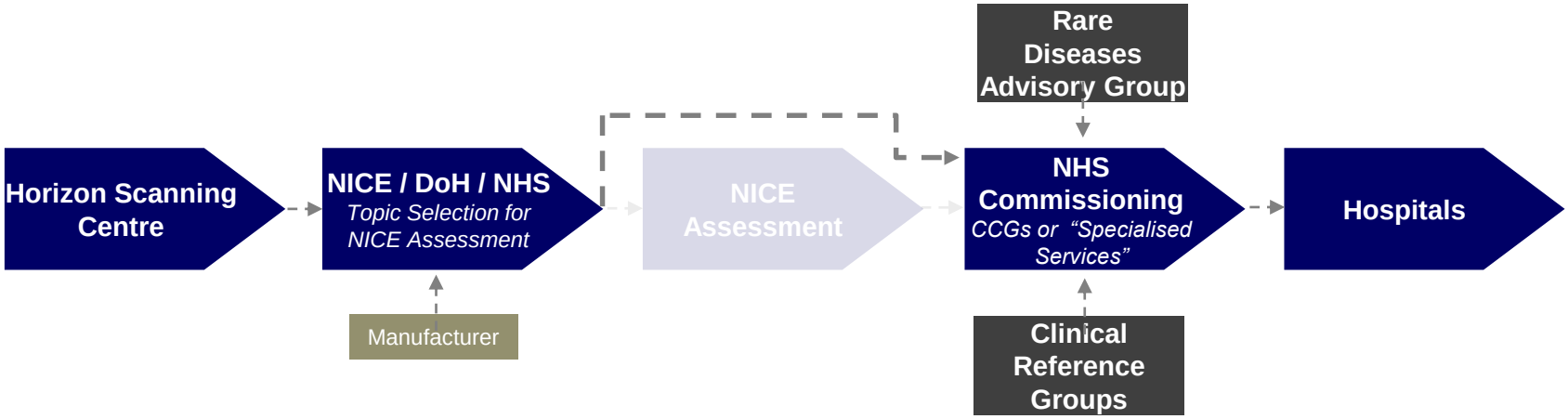
Alternatives

Category	Topic selection by:	Selection criteria	Methodology	Impact on NHS Commissioning
Technology appraisals (TA)	NICE/DoH	HTA selection criteria	Clinical and cost-effectiveness	Result in **binding obligations** for NHS commissioning
Highly Specialised Technologies Evaluation (HSTE)	NICE/DoH	HSTE selection criteria	Incremental QALYs and costs to the NHS and PSS, impact on budget for specialist commissioning, ethical considerations (for therapies with significant benefits for the patient and/or the healthcare system, development/ manufacturing costs may be accounted for)	
Medical Technologies Guidance (MedTech)	Notification by manufacturer	CE marked medical device; New or innovative modification of existing device; by definition, a human cell cannot be a medical device [viable or non viable] Note: ATMPs not eligible	Clinical effectiveness; cost consequence (e.g. cost-savings, cost-neutral)	Drives adoption of resource releasing technologies
Interventional Procedures Guidance (IPG)	Notification by manufacturer/ NHS clinicians	**Therapies introduced into the body in a novel way, normally by an operator**; a cell therapy may undergo both an IPG and a TA or HSTE ; Available data should permit undertaking of assessment	Safety and efficacy	Unlikely that a therapy requiring new IP would be commissioned in the NHS without IPG

Out of ~200 new products launching p.a. only ~25% are assessed by NICE TA or HSTE

- Specific selection criteria apply for NICE TA and HSTE
  - These assessments result in binding obligations for NHS commissioning
- For therapies without formal NICE assessment, NHS England will decide about their commissioning
  - E.g. therapies with very small target population such as ADA-SCID* (~2 new patients p.a. in UK)
    - At first instance **Individual Funding Requests (by individual clinicians and hospitals) to NHS Commissioners** are likely to be required
    - After a number of these requests has been received (>20 nationally or >5 per region), NHS England would proceed with developing a centralised policy for commissioning the service

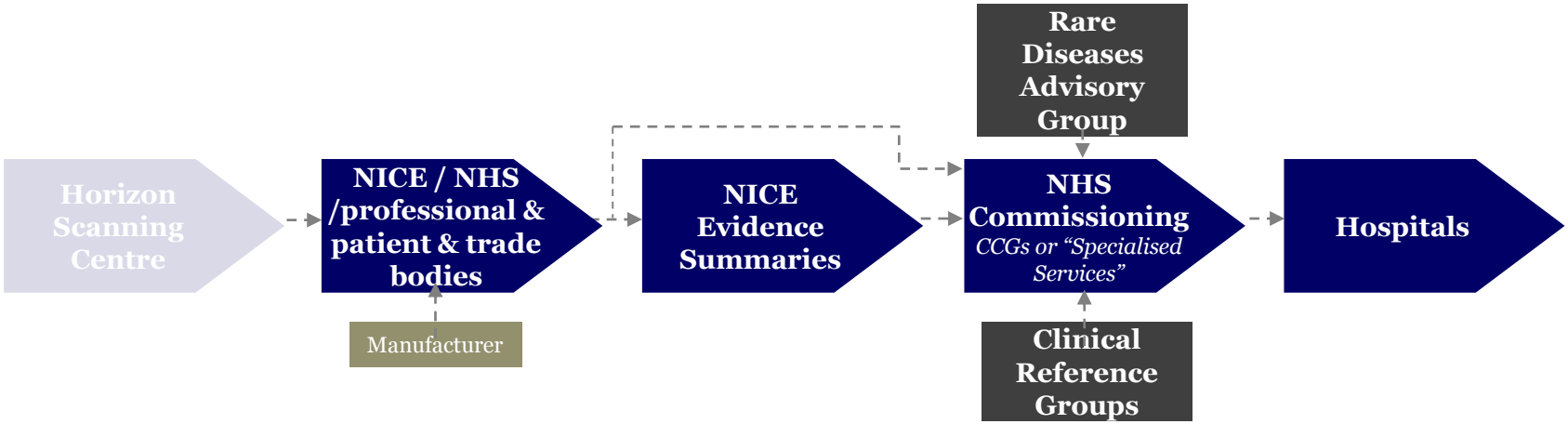
Top-level roadmap to market access for licensed ATMPs (England)



* Adenosine Deaminase Severe Combined Immunodeficiency

Unlicensed therapies do not undergo formal NICE assessment; NICE "*Evidence Summaries*" may be developed instead

Top-level roadmap to market access for unlicensed therapies (England)



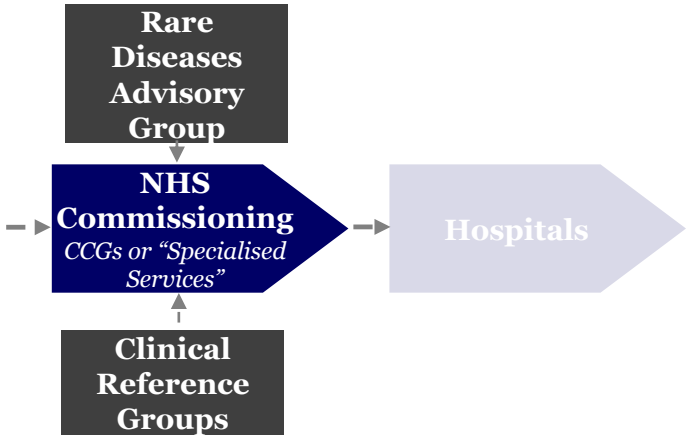
NICE "*Evidence Summaries*" are quality assured summaries of best available evidence that help NHS make informed decisions on commissioning new therapies which lack formal NICE guidance, including unlicensed/off-label therapies.

Whereas unlicensed therapies benefit from lower cost route-to-market, challenges for unlicensed therapies include:

- Weaker defensibility due to lack of data and market exclusivity
- Time-limited option, as it is theoretically contingent on the absence of an equivalent and available licensed product

Commissioning decisions for most cell-therapies in England will be taken by the "Specialised Services" with advice from CRGs (and RDAG in the case of rare diseases)

- Specialised Services (NHS England) are for high cost treatments, provided in relatively few specialized hospital trusts and for small numbers of patients
  - There are 10 Specialised Commissioning Groups (SCGs) that commission specialised services regionally
- Specialised Services cover both licensed and unlicensed therapies; four factors determine inclusion under Specialised Services:
  - Size of target population
  - Cost of service or facility
  - Number of clinicians/hospitals able to provide service
  - The financial implications for CCGs if they were to arrange for provision of the service individually



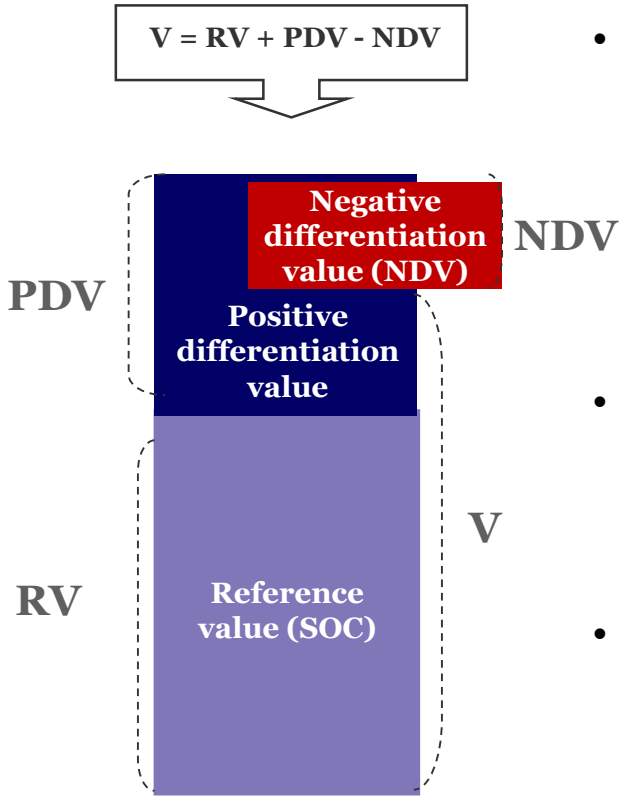
- Clinical Reference Groups (CRGs) advise Specialised Services on commissioning decisions
- For those therapies that target rare diseases there is an additional body that advises on their commissioning: the Rare Diseases Advisory Group (RDAG)*

**Advises NHS England/Scotland/Wales/Northern Ireland*

Globally, pricing approaches in healthcare are shifting towards value-based models

	Cost-based	Competitor-based	Value-based
What is it?	• Price is set by assumptions on costs, expected sales volumes and margins	• Price is driven by the pricing of competitor products	• Price is based upon therapeutic /economic value to the customer
Examples	• Cost-plus pricing • ROI based pricing (e.g. PPRS in UK)	• Penetration pricing • Reference group pricing	• Value-based pricing
Comments	• Becoming obsolete; no longer resonates with payers	• Enforced by many reimbursement systems for "**undifferentiated**" products	• Typical approach for **differentiated** products

Value-based assessment relies on the quantification of the added-value that a new technology delivers over the SOC



- **Reference Value of Standard of Care (SOC)**
  - Comparative data against the SOC is required:
    - H2H comparative data demonstrating superiority or non-inferiority of Product X against the SOC is preferred
    - Indirect comparisons of high methodological standards (NMA) usually sufficient for non-inferiority claims
- **Differentiating Value e.g.**
  - Clinical effectiveness
  - Economic impact: budget impact, cost-minimization, cost-effectiveness, cost-utility
- **Value (V)**
  - For a given indication "V" varies depending on the intervention's positioning in the treatment algorithm & the target patient profile

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In the UK free pricing applies, however NICE assessment influences reimbursable by the NHS price (*applies to licensed therapies with an HTA or HSTE*)

- Free pricing continues to apply under the latest PPRS (Jan 2014 to Dec 2018)
  - PPRS controls* profitability by setting limits on return on capital and return on sales
    - For entire company portfolio rather than individual products
  - Above these limits pay-backs are imposed
- Free pricing supports earlier therapy launch in UK than in price-regulated markets
  - UK price is referenced by multiple countries: high UK list price boosts overseas price
    - Therefore **UK is a market of strategic importance** for manufacturers
- NICE applies value-based-assessment in developing recommendations about a therapy's adoption by the NHS
- Label expansions may result in price reduction
  - if value in new indication is lower than in original

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* Newly launched products and companies with UK sales below £5M p.a. excluded from PPRS profitability controls.

Uncertainties over budget impact, clinical and cost-effectiveness necessitate innovative pricing agreements

Payers are increasingly resistant to budget uncertainties

- Uncertainties arise from:
  - Not well established clinical and cost effectiveness profiles at launch
  - Variation in individual patient needs for dosing and length of treatment
- These have lead to numerous innovative pricing agreements (e.g. “patient access schemes” in the UK)
  - Financially - based
    - Manufacturer offers discounts or rebates
    - Manufacturer changes price (change may be kept confidential)
  - Outcomes - based e.g.
    - If value is proven, price can increase
    - If value is not proven, price will decrease
    - Risk-sharing e.g.
      - Velcade in progressive multiple myeloma: manufacturer rebates the full cost of Velcade for people who, after a maximum of four cycles of treatment, have less than a partial response (defined as reduction of serum M protein by ≤50%) - *NICE TA129*

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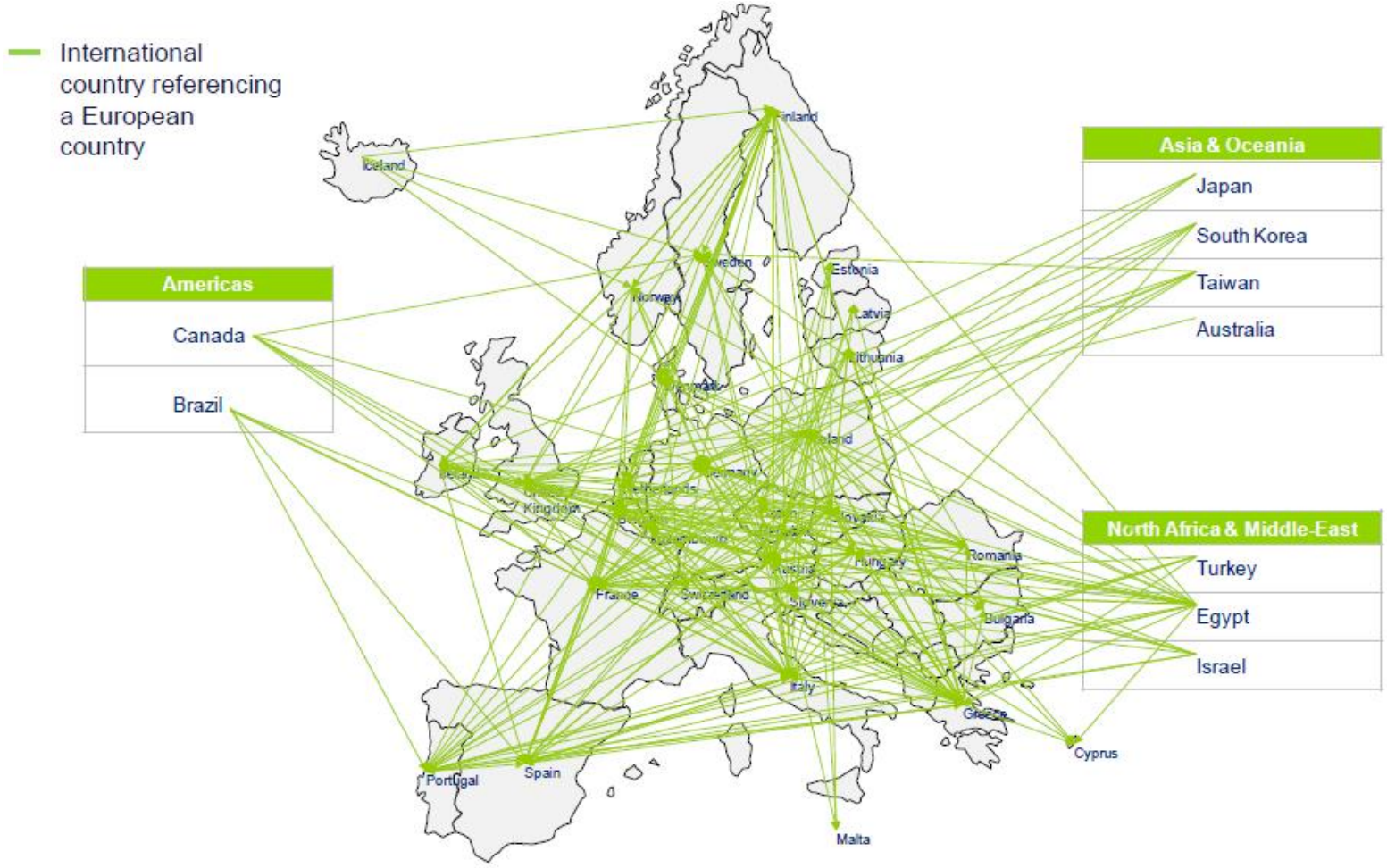
With multiple countries referencing Big5EU prices, these five markets are the focus of market access optimisation activities



Source: Deloitte, Model N, Professional Pricing Society Webinar September 2012

To optimize market access, robust pricing, reimbursement and value communication strategies need to be developed pre-launch

Objectives	• Assess opportunity (e.g. epidemiology, disease burden, unmet need, clinical /pricing benchmarks, funding & supporting data requirements, competition)	• Generate insights on reaction to "Target Product Profile", key value drivers, likely positioning, pricing, reimbursement, uptake, supporting data requirements	• Development of clinical value arguments and economic models • Test value story with key market access stakeholders • Identify areas to strengthen story and data	• Identify revenue maximising target price • Inform asset valuation and market access strategy • Enhance market access potential and strategic partnering	• Compile in a single document clinical and economic value proposition and corresponding evidence to support negotiations

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Dermagraft's launch in the UK exemplifies the implications of a not well-planned market access strategy

- Dermagraft was launched in UK (2002), as a device for diabetic foot ulcers
  - Average treatment cost of £2000/per patient
- Willingness to pay by market access stakeholders was low:
  - Since Dermagraft was positioned as a device, its fair price was benchmarked against conventional dressings
  - There were no comparative data vs a relevant comparator
    - Therefore Dermagraft's incremental value could not be demonstrated
  - Budget impact concerns were exacerbated by not identifying patient subgroups in which the product was most effective
- Dermagraft suffered poor uptake and it was eventually withdrawn from the UK*

Availability of **comparative data vs a premium-priced comparator****, identification of **subpopulations***** where added-value is maximised and development of **health-economic arguments**, could have enhanced market access

* Dermagraft is currently marketed in the US by Organogenesis
** e.g. advanced wound care with growth factors (Regranex)
***e.g. diabetic foot ulcer patients who responded poorly to conventional therapy

Optimisation of supporting data presents challenges that require careful consideration

Challenges	For consideration

• Supporting data limitations e.g.
  • Alignment of data at launch with claims of long-term patient benefits
  • In the case of rare diseases or niche subpopulations within larger therapy areas the following may apply:
  • Small trial populations due to challenging recruitment
  • Limited availability of phase III data (if accelerated clinical development is feasible for MA)
  • Limited availability of comparative data
  • Trial design (single arm vs placebo-controlled vs active controlled) impacts availability and type of comparative data (H2H vs indirect)
  • Surrogate vs. hard endpoints
	• Conditional pricing & reimbursement on post-launch data generation / PAS
	• Adaptive trials
	• Where accelerated development applies, start comparative data collection early
	• Validated strategies for comparative data generation when H2H comparisons through RCTs are not feasible
	• Obtaining joint agreement on optimal endpoints from both regulatory and HTA bodies

Therapy-specific and environmental constraints need to be addressed to harness the opportunity cell therapies present

Challenges	Potential remedies
• High manufacturing costs dictate a price that may be challenging to justify reimbursement on the basis of current ICER thresholds	• Manufacturing process optimisation • Accounting for disease burden and wider societal impact (under consultation)
• Impact of unlicensed therapies on the uptake of licensed ones for the same target population	• Policing the regulatory legislation on specials / hospital exemptions ○ Time limited options contingent on the absence of an equivalent and available licensed product

• Early access scheme
  ○ Such unlicensed therapies have unclear funding mechanism; expected to be manufacturer sponsored
	• Outcomes-based patient access schemes to deal with uncertainty
	• A temporary price is agreed until the formal "post - market authorisation" price is issued
	  ○ Rebate may apply if former price is higher than the latter
	• Cost recovery