Health Economics, Pricing & Reimbursement models for ATMPs in other countries

Agenda

- Overview with presentation topic and short explanation of HTA, and included countries
- Specific HTA cooperations between some of the selected countries.
- Countries in scope are: EU5, Nordics, USA, Canada, NL, Japan, S-Korea and China
- Per country slides with: key take-aways, overview of reimbursement system, approved ATMPS, pricing, stakeholders and trivia/case example

Health technology assessments are used to evaluate the properties and effect of health technologies

Health technology assessment (HTA)

- HTA is the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods.
- All HTA bodies seek value-for-money from medicinal products. However, how this is done by the individual HTA bodies in e.g. EU nations differs in priorities and methods. The degree to which the HTA bodies can influence negotiated prices are linked to their nation's specific health system funding model and the weighting of economic/budget impact versus broader clinical societal impact.
- Some nations' HTA bodies are more willing than others to accept new kinds of evidence beyond traditional randomized controlled trials and to consider economic models that involve extrapolating longer-term benefit from limited existing data.

A health technology is defined as an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation.

Health technologies include pharmaceuticals, devices, procedures and organizational systems used in health care.

Disclaimer

- Information regarding China, Korea and Japan has been collected with the assistance of ABD Life Sciences.
- Information regarding the European countries has been collected with the assistance of Monocl.
- This presentation has been compiled by the Swelife ATMP project participants based in a large part on the contents of the ABD Life Science and Monocle reports.

Reimbursement models and outcomes for ATMPs in other countries

- Especially for SMEs and academic start-ups, that don’t have the support structure from a larger corporate organisation, it is crucial to understand how different countries approach ATMPs

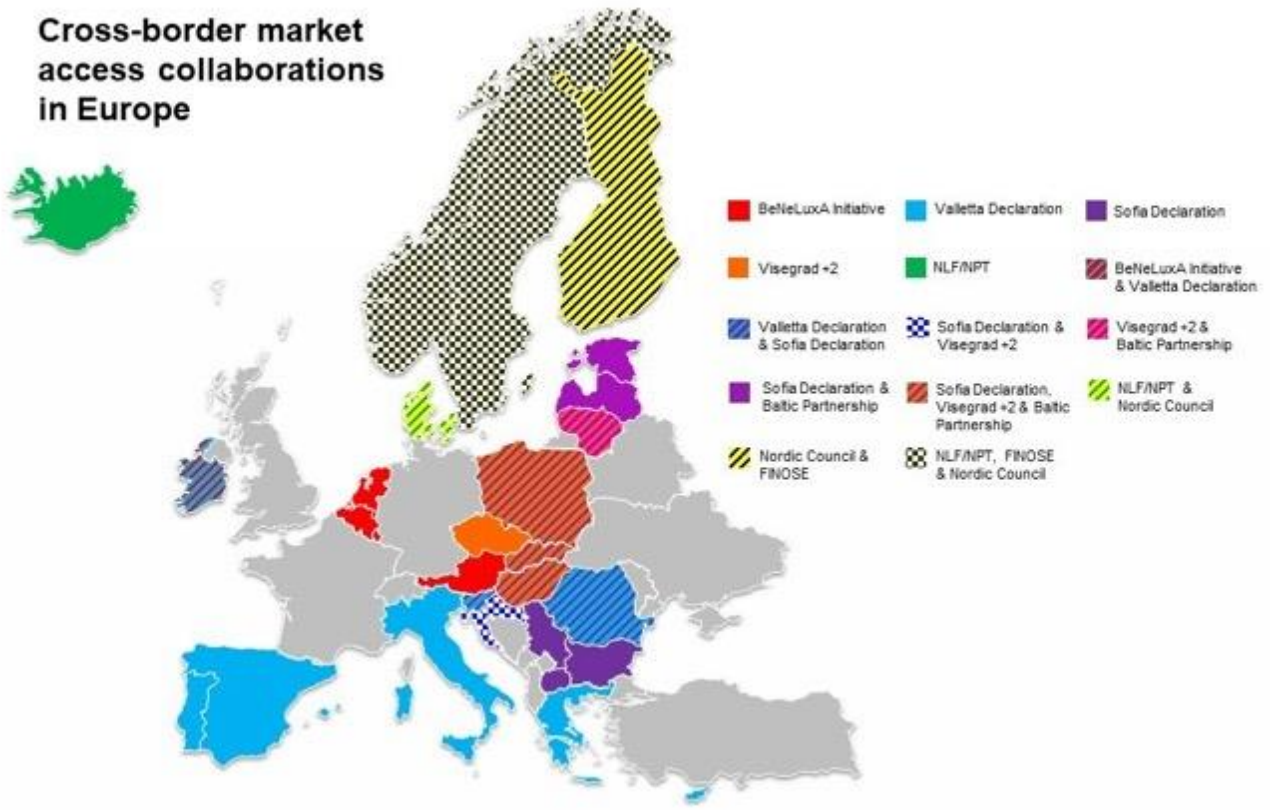
- Goal is to get insights into the country-specific roadmaps and the way different decision makers deal with HE / Pricing and Reimbursement issues

Some of the variables addressed per country

- Reimbursement and pricing process
- Available pricing models e.g. pay-for-performance, risk sharing
- Mapping of the stakeholders and their activities, developing a country-specific roadmap
- Health Economic requirements
- Case example

EU HTA cooperations

- There are several collaborations underway within Europe
    - BeNeLuxAIr (Belgium, Netherlands, Luxembourg, Austria and Ireland)
    - La Valetta Group (Italy, Spain, Greece, Portugal, Slovenia, Cyprus, Malta, Croatia
    - FINOSE (Finland, Norway, Sweden)
    - Visegrad (Czech, Hungary, Poland, Slovakia, Croatia)
- Real live example: collaborative HTA and pricing decision on Spinraza in NL/ BE

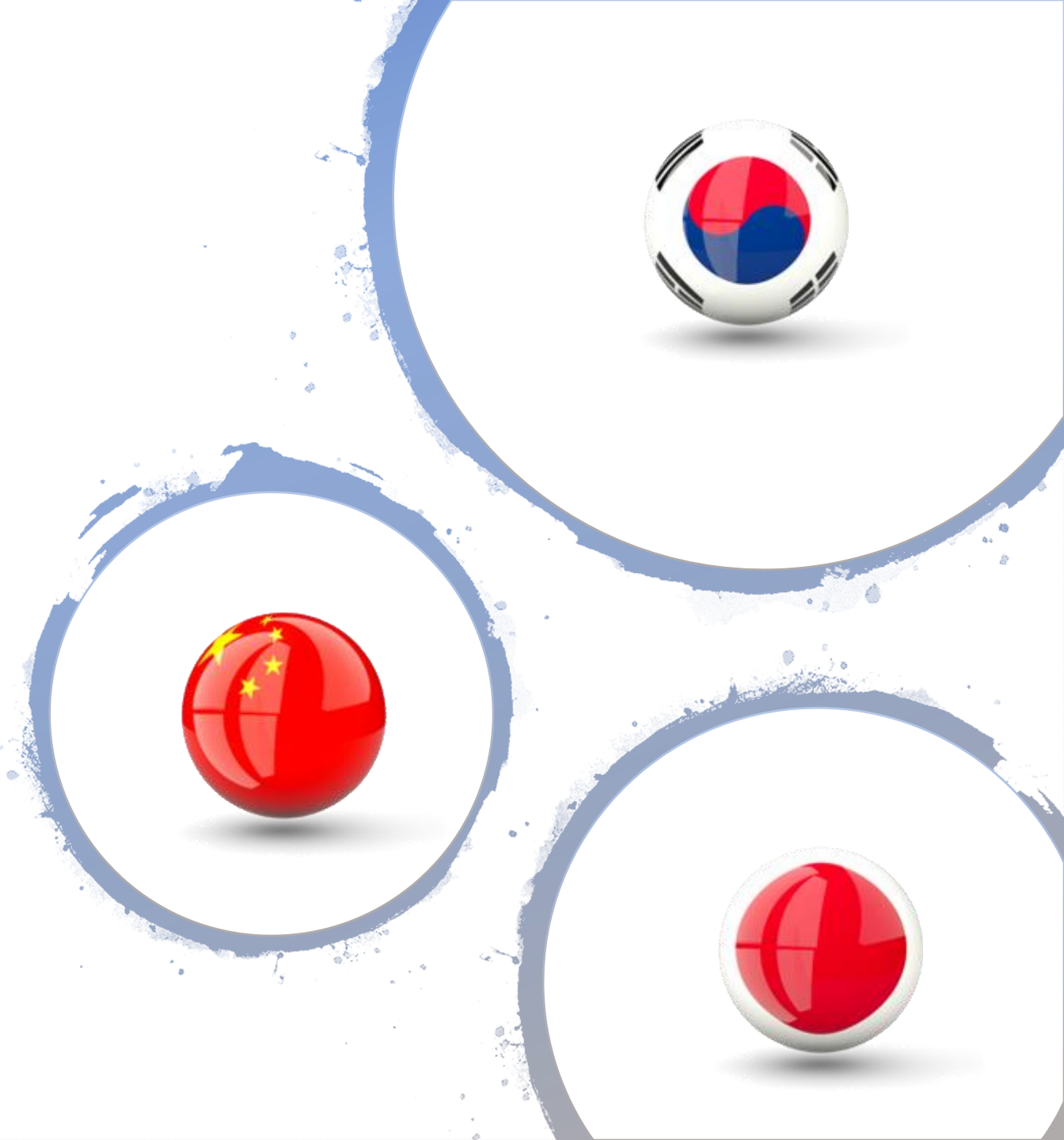


NL – BE Spinraza

- Spinraza (Nusinersen) is a product brought to market by Biogen
- Orphan drug: spinal muscular atrophy
- Official list price of product: 83.300€ per injection, 3-6 injections required per year, e.g. 499.800€ per year.
- Dutch and Belgium governments: current prices deemed unacceptable, initiated joint negotiations in order to come to a more acceptable price point
- First positive international negotiation result on the admission of a new medicine to the basic coverage. This means that Spinraza is reimbursed in the Netherlands and Belgium under comparable financial conditions.

Asia

- China
- Japan
- South Korea



ATMP in China, Japan and South Korea

- Based on report by ABD Life Sciences, finished in July 2019, full report available

- Assignment: overview of hurdles and requirements covering:
  - Business conditions
  - Regulatory affairs
  - Clinical development
  - Manufacturing
  - Price and reimbursement

China

China: executive summary

- Domestic funds available for local development
- Crowded field in certain areas of drug development, such as CAR-T
- Conditional approval possible for very high unmet medical needs
- Large number of treatment naïve patients available for clinical trials
- Prices for innovative drugs/therapies often 50-90% lower vs the West

China - Overview

National HTA organization	China National Medical Products Agency, Ministry of Labor and Social Security
Purposes of HTA	Budgeting, market approval
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

	ATMP technology	HTA assessment of therapy	Type of HTA assessment	Payment method
Gendicine	GTMP	No information available	N/A	Reimbursed, NA
Oncorine	ATMP	No information available	N/A	Reimbursed, NA
Yescarta	GTMP	No information available	N/A	Reimbursed, NA
Keytruda	sCTMP	No information available	N/A	Reimbursed, NA
Alofisel	ATMP	No information available	N/A	Reimbursed, NA
Imlygic	GTMP	No information available	N/A	Reimbursed, NA
Potentially more	?	?	?	?

China: Key Stakeholders

- China National Medical Products Agency, like the FDA and EMA is responsible for market authorization
- Ministry of Labor and Social Security, is in charge of the general BHIS formulary.

- National Development and Reform Commission is responsible for setting prices for BHIS drugs including new drugs.
- The National Health Commission (NHC), is responsible for the overall guidance of healthcare reform, administering China's Essential Drug List (EDL) and managing the drug tendering and procurement policies.
- Provincial Labor and Social Security Authority: Provincial Labor and Social Security Authority can add or remove Tier B drugs on BHIS formulary. The total changes, including adding or removing, should not exceed 15% of Tier B drugs.
- Provincial Pricing Authority is responsible for initial screening of application to set prices higher than NDRC prices. They are also in charge of setting OTC prices, and Tier B formulary drugs adjusted by provincial Labor and Social Security Authority.

China: System

- Centralized system for medical, pharmaceutical and ATMP approval. Medicinal products in China were reimbursed on city, provincial or national level. It used to take several years after commercial launch until a new drug would be in the national reimbursement list, as certain number of local reimbursement approval would be necessary first. This has changed dramatically during the last years with a possibility for innovative therapies to be reimbursed at the national level within a relatively short time period 12- 24 months.

- China National Medical Products Agency, like the FDA and EMA is responsible for market authorization

- Prices have historically be notoriously low; however, new innovative therapies could be launched at any price, which wealthy and privileged patients with private insurances may be able to cope with. The market size would just be much smaller than otherwise anticipated

- Mix of private and public insurance schemes for patients

China: HTA and Reimbursement system

- BHIS (basic health insurance scheme) formulary is maintained by the Ministry of Labor and Social Security
- In China, the National Development and Reform Commission (NDRC) is responsible for setting ceiling retail prices for BHIS formulary drugs. No drugs on BHIS formulary can be dispensed with a price higher than the published retail prices.
- China has sped up reimbursement decision and listing as well as including innovative biologics and small molecules. Furthermore, China has invited foreign companies to submit innovative therapeutics for local approval through a high priority, Fast Track approval process, to mitigate serious gaps in accessibility of new medicines and take care of unmet medical needs.
- Local and foreign companies launching new treatments on Chinese market without being reimbursed often offer patient access programs.

China: Specific dossier requirements

- **Below some suggestions from experienced industry insiders that have made several submissions in China to start clinical trials and to get market approval to start commercialization.**
- Translation into simplified Chinese by experienced regulatory affairs personnel with true bilingual ability. Chinese language frequent use of idiomatic expressions and erroneous translation are common especially by Chinese educated abroad returning in China after many years in the West
- Submit applications written both in English and Chinese using a disclaimer that “in case of doubt, the English version shall prevail”. It will effectively double the size of a submission but remove any concerns from HQ regarding correct wordings in the submissions
- Make sure all data from EU and US are included and well explained
- Typically, there are requirements by CDE of additional toxicology data compared to EMA and USFDA
- Formal consultations with NMPA and CDE is possible, but only in Chinese!

China: case example

- Hengrui's Chinese developed programmed cell death 1 (PD-1 drug)
- Received Conditional approval for the Chinese market for the treatment of relapsed or refractory classical Hodgkin lymphoma
- Jiangsu Hengrui spent 504.31 million Chinese yuan on the research and development of camrelizumab, conducting more than 50 clinical trials on the drug for 12 indications, including liver cancer and lung cancer.
- Priced at 19,800 yuan (2500 EUR) per vial in China, making it more expensive than Bristol-Myers Squibb Co.'s blockbuster Opdivo as well as domestic competitors.
- Now covered conditionally by a patient access programme somewhat cutting prices to those who have access
- The scheme can be summarized as "Buy two, get two free; buy another four, get one year free". This means enabling eligible patients who pay for 2 medication cycles to receive 2 more free of charge, and then once purchasing 4 more medication cycles will receive a one-year course of treatment (capped at 18 shots) also free of charge

恒瑞®

Hengrui Medicine

Japan

Japan: Executive Summary

- Large interest in “Regenerative Medicine”, nearly all major domestic pharma companies invest in this area
- PMDA (Japanese EMA/FDA first authority with conditional and time-limited approval of ATMPs after explorative Phase 2 studies.
- Priority review and accelerated development: SAKIGAKE.
- Price level for ATMPs lower than US, more comparable with Europe
- It is important to note that Japan does not use pharmaco-economics calculations to set prices for treatments. Furthermore, prices are typically reduced every two years. Thus, it is important to enter the market with a high price.

Japan: Overview

National HTA organization	Pharmaceutical & Medical Device Agency (PMDA)
Purposes of HTA	Clinical practice guidelines and protocols, planning and budgeting
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Type of HTA assessment	Payment method
Temcell	STMP	NA	Single technology assessment (STA)	No advanced payment method
Kymriah	GTMP	NA	Single technology assessment (STA)	No advanced payment method
Stemiras	sTMP	NA	Single technology assessment (STA)	No advanced payment method
JACE/JACC	sCTMP	NA	Single technology assessment (STA)	No advanced payment method
Collategen	GTMP	NA	Single technology assessment (STA)	No advanced payment method
Heart Sheet	STMP	NA	Single technology assessment (STA)	No advanced payment method
Stemirac	STMP	NA	Single technology assessment (STA)	No advanced payment method

Japan - Key stakeholders

- Pharmaceutical & Medical Device Agency (PMDA)
- Ministry of Health, Labor and Welfare (MHLW)

Japan - System

- Centralized system for medical, pharmaceutical and ATMP approval. System is highly organized and at par with systems in European countries.

- Japanese authorities require Phase 1 safety and PK data in Japanese patients before Japan can join any dose-response or efficacy study. There is always a possibility of simultaneous approval in EU, US and Japan.

- PMDA consultation are always recommended and there is a specific group handling ATMPs. The fees are high, typically between EUR 30,000 and 50,000 to PMDA. There are two types of consultations:

I. "R&D Strategy" including Quality and non-clinical Safety prior to or during the pre-clinical development work.

II. "R&D Strategy Pre-Phase 1" before the clinical trials starts in Japan.

Japan – HTA and Reimbursement

- Prices for therapies in Japan are set with references to similar products on the Japanese market. If it is a novel therapy, prices in the three leading EU-markets (France, Germany and UK) are used as reference.
- It is important to note that Japan does not use pharmaco-economics calculations to set prices for treatments. Furthermore, prices are typically reduced every two years. Thus, it is important to enter the market with a high price.

- Japan has one national public health insurance covering almost all of the population. Everyone contributes by paying premiums either directly or through their employers. Patient co-payment is up to 30% of the total cost up to a monthly cap. The High-Cost Medical Expense Benefit System subsidizes medical costs in excess of monthly, out-of-pocket (OOP) thresholds.

- Ongoing discussions regarding the impact of some high-cost ATMPS on the affordability of the healthcare system.

Japan - Sakigake (accelerated approval

- The Japanese version of “priority review” and “accelerated approval” scheme through what in Japan is called “Sakigake”. This would allow for premium pricing later on.
- “The Pharmaceutical, Medical Device and Other Therapeutic Products Act” (PMDA) that came into effect in November 2014 has enabled development of ATMPs with a possibility to come to the market more swiftly if they address high unmet medical needs.

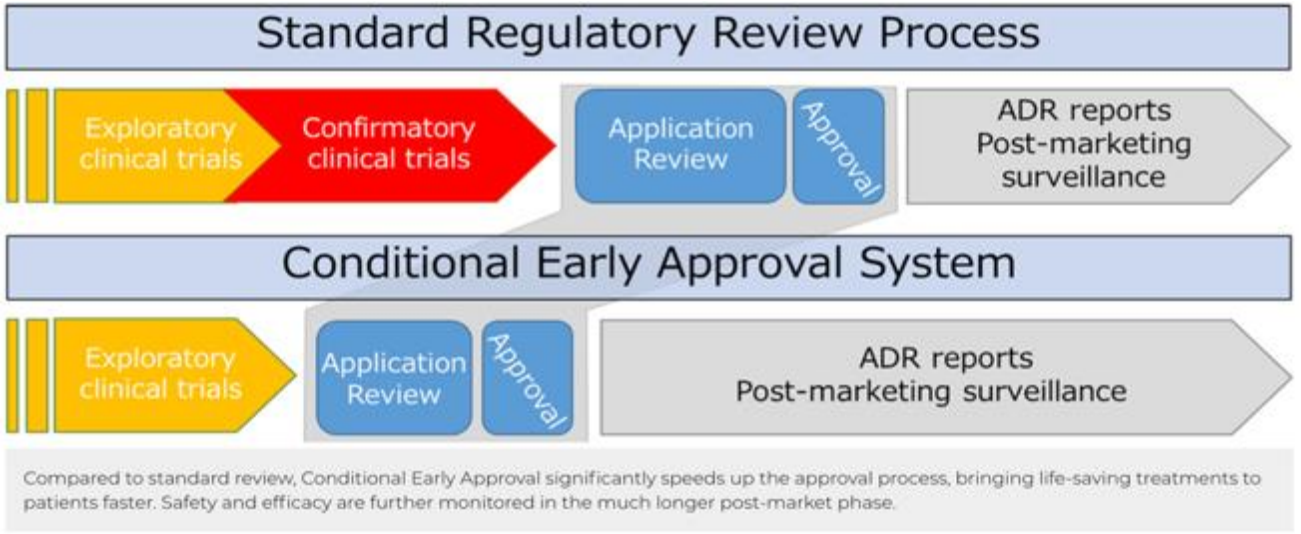
- Japan’s PMDA set up a team for sakigake fast-track review system
  - Review timeline approx. 6 months

- Innovative and new ATMP’s developed to address high unmet medical needs, especially in rare and orphan diseases could get conditional / time-limited approval after Phase 2 Explorative-studies. However, Phase 3 confirmatory studies need to be completed with primary endpoints reached within 5 years of the conditional / time-limited authorisation.

Japan - Sakigake (accelerated approval)

- Japan introduced the “SAKIGAKE” designation scheme on a pilot basis in 2015, aiming to accelerate the time to market for innovative drug candidates by giving them a series of privileges in both the pre-application and review process. To be eligible, candidate drugs need to clear four criteria:
  - being novel
  - targeting serious diseases
  - having prominent efficacy
  - being developed and planned for approval in Japan ahead of the rest of the world, or at least simultaneously with other major markets.
- To shorten time to approval as well as to facilitate R&D, Sakigake-designated drugs will be entitled to
  - prioritized consultation
  - extensive pre-application consultation
  - priority review
  - extensive handholding from review partner
  - possible extension of re-examination period (data protection period) up to 10 years

- With the PMDA’s pre-application consultation services intended to speed up approval review, the total review time (from application filing to approval) for designated products is expected to be six months compared with the typical 12 months. Once approved, Sakigake-designated products will be eligible for a premium on their reimbursement prices, called the Sakigake premium.



Japan: case example

- TEMCEL, Mesenchymal stem cell-based product for acute graft-versus-host disease
- Produced by JCR pharmaceuticals (in cooperation with Mesoblast
- The product was approved in September 2015 as Japan's first allogeneic regenerative medical product and launched in February 2016.
- The Japanese Government's National Health Insurance set reimbursement for TEMCELL at ¥868,680 (around 7,200 Euro) per bag of 72 million cells. It is expected that a patient will recive between 16 and 24 of these bags. Which means that treatment cost is between ¥13,898,880 and ¥20,848,320 (115,600.- 173,500 EUR)
- National reimbursement was granted using phase I and II date with promise of phase III follow-up

JCR Pharmaceuticals Co.,Ltd.

South Korea

South Korea – Executive summary

- Large number of ATMPs from domestic companies approved.
- Several scandals are dampening the enthusiasm
  - Latest scandal: Kolon Life Sciences forced to withdraw cell therapy product Invossa: contained kidney cells, not cartilage cells as specified!
  - MFDS has promised increased scrutiny; same promise as after the great stem cell scandal in 2006 (fabrication of experimental data)
- MFDA may grant priority review and issue conditional approval
- Pricing levels have been lower than in Japan

South Korea – Executive summary

National HTA organization	Ministry of Food and Drug Safety (MFDS
Purposes of HTA	Clinical practice guidelines and protocols, planning and budgeting
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Type of HTA assessment	Payment method
ImmuneCell-LC	STMP	N/A	Single technology assessment (STA)	No advanced payment method
CreaVax	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Adipocell	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Caristem	STMP	N/A	Single technology assessment (STA)	No advanced payment method
HeartiCellgram	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Chondrom	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Cupistem	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Holoderm	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Hyalograft-3D	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Kaloderm	STMP	N/A	Single technology assessment (STA)	No advanced payment method
KeraHeal	STMP	N/A	Single technology assessment (STA)	No advanced payment method
Queencell	STMP	N/A	Single technology assessment (STA)	No advanced payment method

South Korea – Key stakeholders

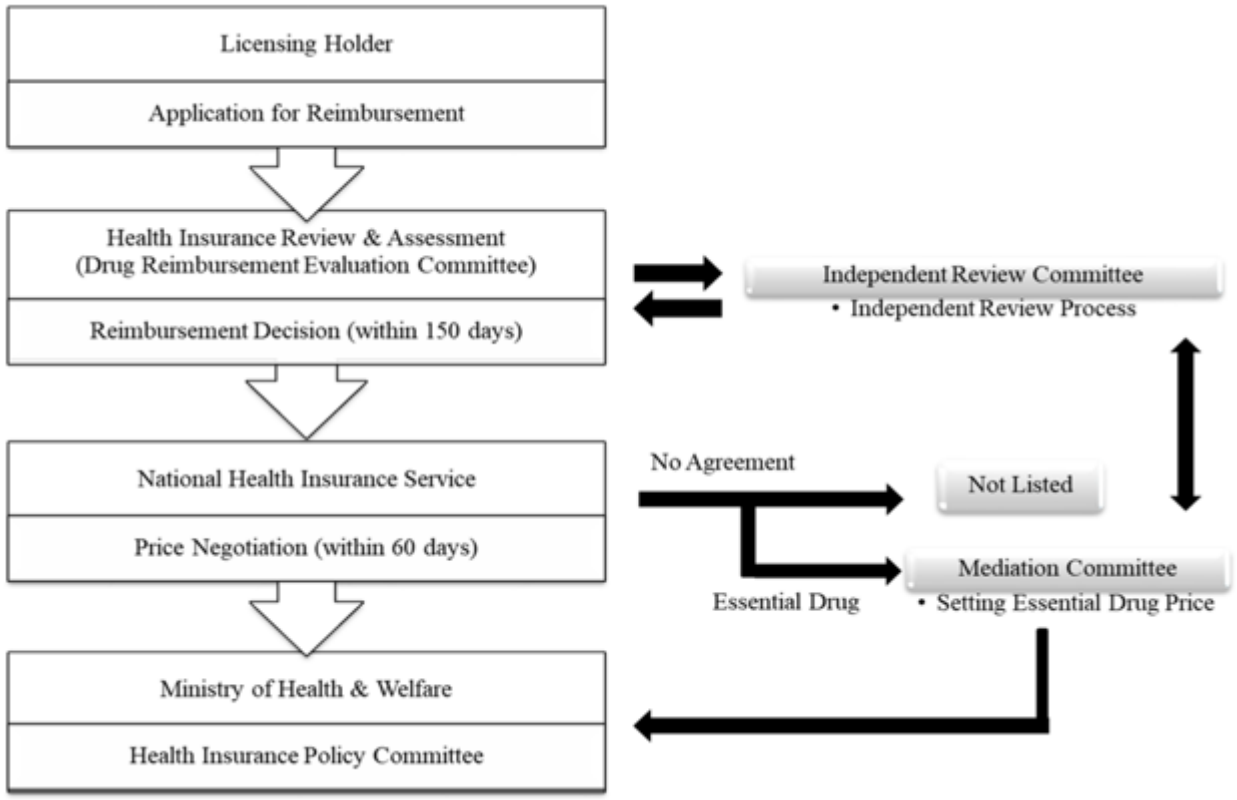
- Ministry of Food and Drug Safety (MFDS). In 2017, there were roughly 1,800 employees at MFDS including all the regional offices, whereof 420 with National Institute of Food and Drug Safety Evaluation (NIFDS)

- National Health Insurance (NHI) is a single payer program reimbursing medical products, but not all and not always 100%

- The Health Insurance Review and Assessment Service (HIRA), determines a therapy's reimbursement level

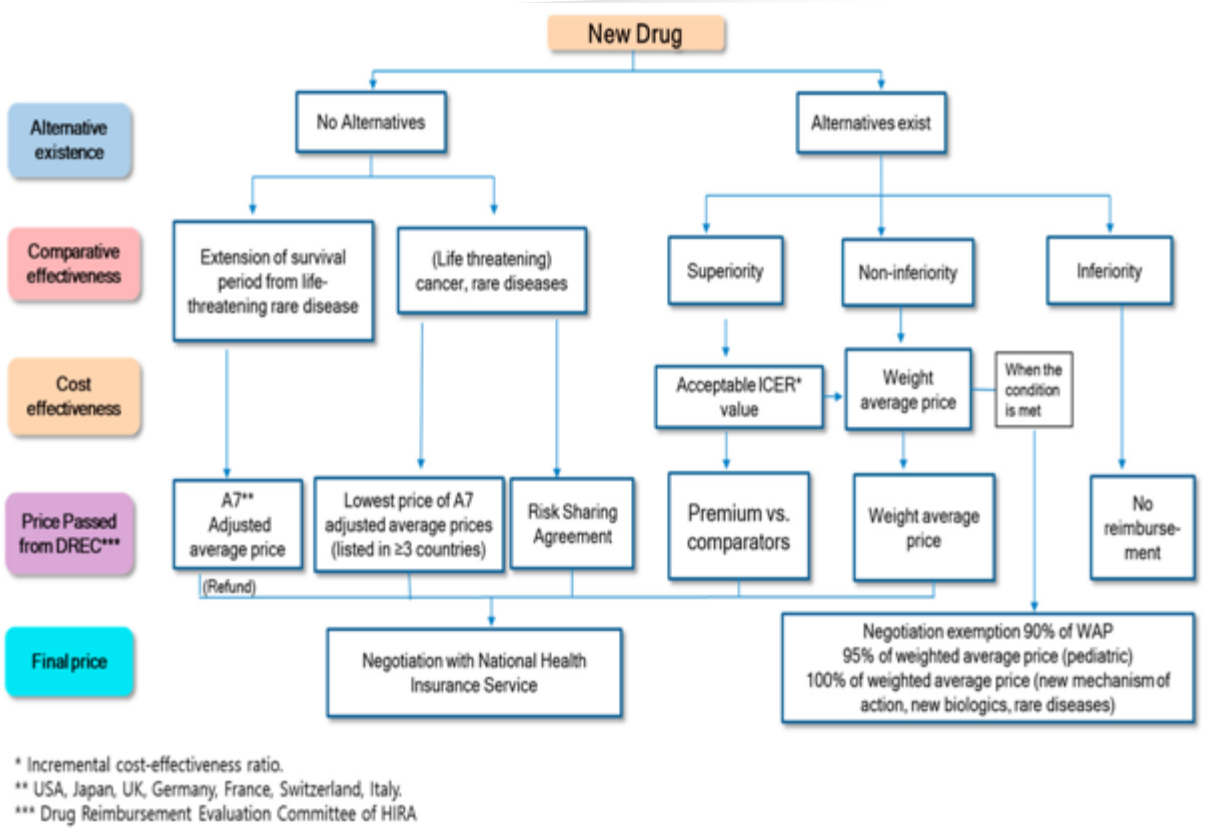
South Korea – System

- National Health Insurance (NHI) is a centralized single payer program reimbursing medical products, but not all and not always 100%
- The Health Insurance Review and Assessment Service (HIRA), determines a therapy's reimbursement level
- HIRA make an assessment within 150 days of application
- NHI determines the maximum price via negotiation within 60 days
- MoHW reviews and announces the price to the public within 30 days



South Korea – HTA and Reimbursement

- South Korea is promoting and prioritising cost innovative therapies moving away from generics. Every manufacturer must provide pharmacoeconomic evidence to show clinical - cost benefits, budget impact based on expected sales, international reference price and the general impact on public health to determine reimbursement.
- National Health Insurance (NHI) is a single payer program reimbursing medical products, but not all and not always 100%.
- Price example of ATMPs (cell therapy products) approved and marketed in South Korea, shows low to moderate pricing:
- Caristem by Medport, USD 19,000 – 21,000
- Cupistem by Anterogen, USD 3,000 – 5,000 per treatment
- Hearticelgram by FCB Pharmicell USD 19,000



* Incremental cost-effectiveness ratio.
** USA, Japan, UK, Germany, France, Switzerland, Italy.
*** Drug Reimbursement Evaluation Committee of HIRA

South Korea: case example

- Caristem, the Allogeneic Umbilical Cord Blood-derived Mesenchymal Stem Cell drug, is for the treatment of knee cartilage defects in patients with Osteoarthritis (ICRS grade IV) caused by degeneration or repetitive trauma.
- Produced by Medport
- Approved commercial use by the Ministry of Food & Drug Safety in January 2012.
- Priced at 17,000 – 21,000 EUR (per knee, excluding other fees)
- Approval based on clinical trial with approx. 80 patients

General advice for China, Japan and South Korea

- “Know what you don’t know”.
- Cultural differences: key hurdle delaying and preventing entry into these markets.
- If these markets are new, need expert on-the-ground support, advice and introductions
- People are key! Establish and build relationships, create mutual trust and understanding, think long term.
- List your Unique Selling Points (USP) and Key Differentiating Factors (KDF), be open, listen and update!
- Try to obtain the true market demand, never rely on assumptions!
- Perform regulatory gap-analysis, and develop mitigation plan to handle risks – “Anything could happen”!
- Do not lose technology due to naïvety and carelessness.

Europe

- Norway
- Denmark
- Finland
- Germany
- The Netherlands
- France
- UK
- Spain
- Italy

Europe: introduction

- All the selected European countries have their own HTA bodies, which may have different priorities and methods, influencing the assessment outcomes. In some countries, more than one HTA body, or several regional HTA bodies (e.g., Italy and Spain).
- No HTA bodies have specialized ATMP committees. General lack of established mechanisms to capture benefit of ATMPs. May lead to risk of ATMP therapies not reaching patients in a timely manner.
- Most of the approved ATMPs have undergone HTA evaluations. So far only small number of products, thus, general reimbursement strategies in Europe still not clear. Also, ongoing debate about whether current HTA methods are best suited for the appraisal of ATMPs.
- Emerging payment models: conditional reimbursement, pay-for-performance and annuity-based payment models, with some countries (e.g. Italy, Germany) more progressive in trying out new models. Discrepancy in reimbursements between the countries.
- The European Commission adopted a new proposal in 2018 regarding HTA. Aim: to strengthen EU-level cooperation among Member States for assessing health technologies.

ATMPs in Europe

- The European Parliament introduced the concept of ATMPs in 2007, triggering the creation of the European Medicines Agency's Committee for Advanced Therapies (CAT). In the US, FDA has created Center for Biologics Evaluation and Research (CBER) dedicated for ATMPs.

ATMPs in EUROPE,
end of Q3 2019

Phase	Number
Marketed	10
Phase 3	177
Phase 2	259
Phase 1	61

ATMPs classification (EU CAT):

- Gene therapy medicines (GTMP): insertion of 'recombinant' genes into the body; leading to therapeutic, prophylactic or diagnostic effect; diseases include genetic disorders, cancer or long-term diseases. Recombinant gene: a stretch of laboratory-created DNA that brings together DNA from different sources.
- Somatic-cell therapy medicines (sCTMP)("cell therapy"): cells or tissues manipulated to change their biological characteristics, OR cells or tissues not intended to be used for the same essential functions in the body; can be used to cure, diagnose or prevent diseases.
- Tissue-engineered medicines (TEP): cells or tissues modified to repair, regenerate or replace human tissue

There are ten approved ATMPs in Europe with a centralized license

- The EMA has a centralized marketing authorization process and one license is valid in the entire European Union. From start to finish, the authorization procedure takes 210 days with a stop-clock after the primary evaluation.
- New therapies are reviewed by different committees in the EMA where the Committee for Advanced Therapies (CAT) drafts an opinion and the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on a potential market authorization.

MARKETING AUTHORIZATION OF ATMPs

Pre-submission

The primary evaluation last between day 0-120.

Secondary evaluation

The secondary evaluation last between day 121-210.
An opinion is created by an EMA committee and the decision is made by the European commission.

Approval

After the approval, post authorization activities begin.

10 ATMP approved in Europe, 17 in the USA

	Brand name	MA date			Status
Gene therapies	*Glybera*	*Oct 2010*	*Hyperlipoproteinemia type I*	uniQure	*Withdrawn*
	Imlygic	Dec 2015	Melanoma	Amgen	Authorized
	Strimvelis	May 2016	SCID	Orchard Therapeutics	Authorized
	Kymriah	Sep 2018	Relapsed or refractory DLBCL & B cell precursor ALL	Novartis	Authorized
	Yescarta	Sep 2018	Relapsed or refractory DLBCL and PMBCL	Gilead Company	Authorized
	Luxturna	Nov 2018	Retinal disease	Spark Therapeutics	Authorized
	Zynteglo	Jun 2019	Beta thalassaemia in patients	BlueBird	Authorized
Cell therapies	*Provenge*	*Sep 2013*	*Prostatic neoplasms*	Dendreon Pharmaceuticals	*Withdrawn*
	Zalmoxis	Aug 2016	HSCT adjunctive treatment	MolMed	Authorized
	Alofisel	Mar 2018	Rectal fistula	Takeda	Authorized
	Chondrocelect	*Oct 2009*	*Cartilage diseases*	TiGenix	*Withdrawn*
	Maci	*Jun 2013*	*Fractures, cartilage*	Vericel	*Withdrawn*
Tissue-based therapies	Holoclar	Feb 2015	Corneal diseases	Chiesi Farmaceutici	Authorized
	Spherox	Jul 2017	Cartilage diseases	CO.DON	Authorized

- There are 10 ATMP approved in Europe by EMA, compared to 17 in the US.
- Four products have been withdrawn from the market.
- Latest to get approved was Bluebird gene therapy Zynteglo.

The centralized committee CAT in EU covers scientific areas relevant to advanced therapies

The Committee for Advanced Therapies (CAT) is the European Medicines Agency's (EMA) committee responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.

- Participates in certifying quality and non-clinical data for SMEs developing ATMPs and in providing scientific recommendations on classifications of ATMPs
- Contributes to scientific advice, in cooperation with the Scientific Advice Working Party (SAWP)
- Takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance or risk-management systems for ATMPs
- Advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy
- Assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs
- Provides scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs
- Supports the work programs of the CHMP working parties

Health technology assessments are used to evaluate the properties and effect of health technologies

- All HTA bodies seek value-for-money from medicinal products. However, how this is done by the individual HTA bodies in EU nations differs in priorities and methods. The degree to which the HTA bodies can influence negotiated prices are linked to their nation's specific health system funding model and the weighting of economic/budget impact versus broader clinical societal impact.
- Some nations' HTA bodies are more willing than others to accept new kinds of evidence beyond traditional randomized controlled trials and to consider economic models that involve extrapolating longer-term benefit from limited existing data.

HTA bodies have not yet established mechanisms to capture the benefits of ATMPs

- ATMPs are associated with high up-front cost compared to traditional treatments, caused in part by complex processes for manufacturing and administration, but primarily due to the long-term value to patients, society, and health systems and administration provided by a one-time treatment.
- Little of the value of ATMPs, which may come over time in terms of savings on treatments and procedures that are no longer necessary and in terms of quality of life and productivity, can be adequately captured in current value-assessment frameworks.
- Because of the nature of ATMPs, many of them may not have developed the comparative evidence versus standard of care at time of launch which HTA bodies traditionally require. The HTA bodies do not yet have a specialized committee with dedicated expertise in ATMPs like CAT, which creates an expertise gap within HTA bodies.
- Most payers and HTA bodies have not established specific mechanisms to adequately capture the full benefits of ATMPs. Consequently, there are many systematic barriers that may hinder ATMPs from reaching patients in need in a timely manner.
- Specific pathways that help ensure ATMP treatments to reach those in need as quickly and safely as possible need to be established. This requires new approaches to measuring value for ATMPs, akin to the innovative and potentially transformative impact that ATMPs can give.
- These approaches also have to offer payers affordable, risk-mitigated means of funding ATMPs, with evidence-based reassurance that healthcare systems are getting value for money and with the commitment to the generation of long-term evidence.

Individual HTA bodies in the EU have different priorities and methods in their assessments

Country/HTA Agency	Method driving HTA recommendations	HTA perspective (economic analysis)	Value judgement			Degree of influence on price/rebate
			Clinical benefit	Cost-effectiveness analysis	Budget impact	
France / HAS (TC, CEESP)	Mixed model: usually clinical, in some cases health economic	Payer (collective perspective)	High	High*/1	High 1	Moderate (benefit tier determines reimbursement level)
Germany / IQWIG (consultative), G-BA	Clinical model (G-BA)	Payer (only drug budget impact)	High	Low 1	Low	High (decision influences pricing negs.)
Italy / AIFA, regions	Mixed model: clinical for national decisions, sometimes health economic at regional level	Payer	High	Low	High/ Moderate	High — AIFA and regions negotiate prices
Spain / SGCMPS, regions	Mixed model: clinical for national decisions, sometimes health economic at regional level	Payer	High	Low	High	High — central and regional negotiations; ref. pricing
UK / NICE (England), SMC (Scotland)	Health economic model[2]	National health system and personal social services	High	High	Low	Moderate-High[2]

The table is adapted from Alliance for Regenerative Medicine's (ARM) consensus report on "Recommendations for Timely Access to Advanced Therapy Medicinal Products in Europe" based on ARM's primary research.

*No formal threshold; 1) only in certain cases/products; 2) clinical aspects are taken into consideration during the process and fed into the HE model.

HAS: Haute Authorité de Santé, IQWIG: Institute for Quality and Efficiency in Health Care, G-BA: Federal Joint Committee, AIFA: Italian Medicines Agency, SGCMPS: General Subdirectorate of Quality of Medicines and Health Products, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium

Innovative payment models have been proposed, but challenges exist that halt the implementation

Reimbursement models

- There are several new payment models, such as conditional reimbursement, pay-for- performance, and annuity-based payments recommended under evaluation for ATMP.
- Conditional reimbursement is an agreement consisting of reimbursement linked to the collection of post-launch evidence, such as Real-World-Evidence (RWE).
  - After collecting prospective population-level evidence from a pre-specified study, the reimbursement is reassessed and there is a possibility to either expand or withdraw the coverage.
  - This coverage evidence development (CED) can be applied when novel medical technologies are promising, yet additional evidence is required to make an informed decision.
  - Increasingly considered as a useful policy instrument since it allows collection of evidence regarding effectiveness and cost-effectiveness of new technologies without delaying market access.
- Several payment models that can be used together with conditional reimbursement have been proposed. Description and challenges associated with them are presented to the right.

PAYMENT MODELS AND THEIR CHALLENGES

	Payment details	Challenges
Annuitized payments	Payments spread over years to overcome affordability issues and soften “sticker shock” regardless of performance.	One-time hit avoided, but long-term budget impact remains unchanged. Patient might leave plan.
Pay-for-performance	Payment only initiated if predetermined goals are met or rebate issued if goals are missed.	Need to define and track long-term outcomes.
Annuitized payment + Pay-for-performance	Similar to annuitized payments, but payment only sent if treatment goals are met.	Need to define and track outcomes long-term. Patient might leave plan.
Discount based on % paid up-front	Payment is spread over time, but payer receives a discount based on initial payment percentage.	Does not protect from risk of treatment failure.

Highlights from nation-specific HTA practices and ATMP market access

- Several of the analyzed countries, such as France, Spain and Italy, have more than one body conducting HTA. For example, one body is responsible for pharmaceuticals and the other for medical devices. In some countries, there are additionally regional authorities that conduct HTA (e.g., Italy and Spain).
- HTA are used to give guidance for approval and/or reimbursement but their influence on approval decision, labelling and price differs between the countries. In Norway, Denmark, Finland, UK, Spain and Italy, the HTA bodies have a more advisory role whereas decision-makers in the Netherlands and Germany are bound to follow the guidance from HTA bodies.
- None of the HTA bodies analyzed in this study have specialized committees with dedicated expertise of ATMPs in place.
- There are many different versions of HTA in use in the selected countries. Within a country, there may be different types of HTA being done, as in Norway, where there are HTA formats; mini-HTA, STA (single technology assessment and full HTA.
- Several countries have started introducing more advanced payment and pricing models for advanced and very cost intensive therapies like ATMPs. For example, there are several versions of pay-for-success or result as an alternative to a more straight-forward reimbursement with a list price in use. Italy is one nation that stands out, but also Spain and Germany have introduced alternative payment models.
- The Finnish government introduced conditional reimbursement in 2017. This is a risk-sharing model for new drugs with limited study evidence and user experience.

Norway

Norway: executive summary

- Norway uses a centralized approach to HTA and reimbursement issues
- Currently no specific pathway for ATMP available
- Norwegian Medicines Agency is key decision maker
- Norway uses a health economic evaluation which takes a societal perspective with indirect costs of treatment and illness into account.
- Wealthy country, relatively strong purchasing power and available budget

Norway - Overview

National HTA organization	The National System for Managed Introduction of New Health Technologies within the Specialist Health Service */Nye Metoder*
Purposes of HTA	Clinical practice guidelines and protocols, planning and budgeting
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Type of HTA assessment	Payment method
Imlygic	GTMP	Uncertain whether Imlygic fulfils the conditions to be recommended for implementation.	Single technology assessment (STA)	No advanced payment method
Kymriah	GTMP	Estimated gain too uncertain. Additional follow-up data needed to evaluate and reduce the uncertainty.	Single technology assessment (STA)	No advanced payment method
Yescarta	GTMP	Estimated gain too uncertain. Additional follow-up data needed to evaluate and reduce the uncertainty.	Single technology assessment (STA)	No advanced payment method
Alofisel	sCTMP	Not cost-effective enough given the severity of patient group.	Single technology assessment (STA)	No advanced payment method

Norway – Pricing and HTA methodology

Pricing

- The Norwegian Medicines Agency is responsible for setting maximum prices on prescription-only-medicines. The agency also evaluates and decides whether a medicinal product should be publicly funded.
- Denmark, Norway and Iceland have started working together to negotiate prices on expensive pharmaceuticals.
- **We have not identified any new type of pricing model for approved the ATMPs.**

HTA

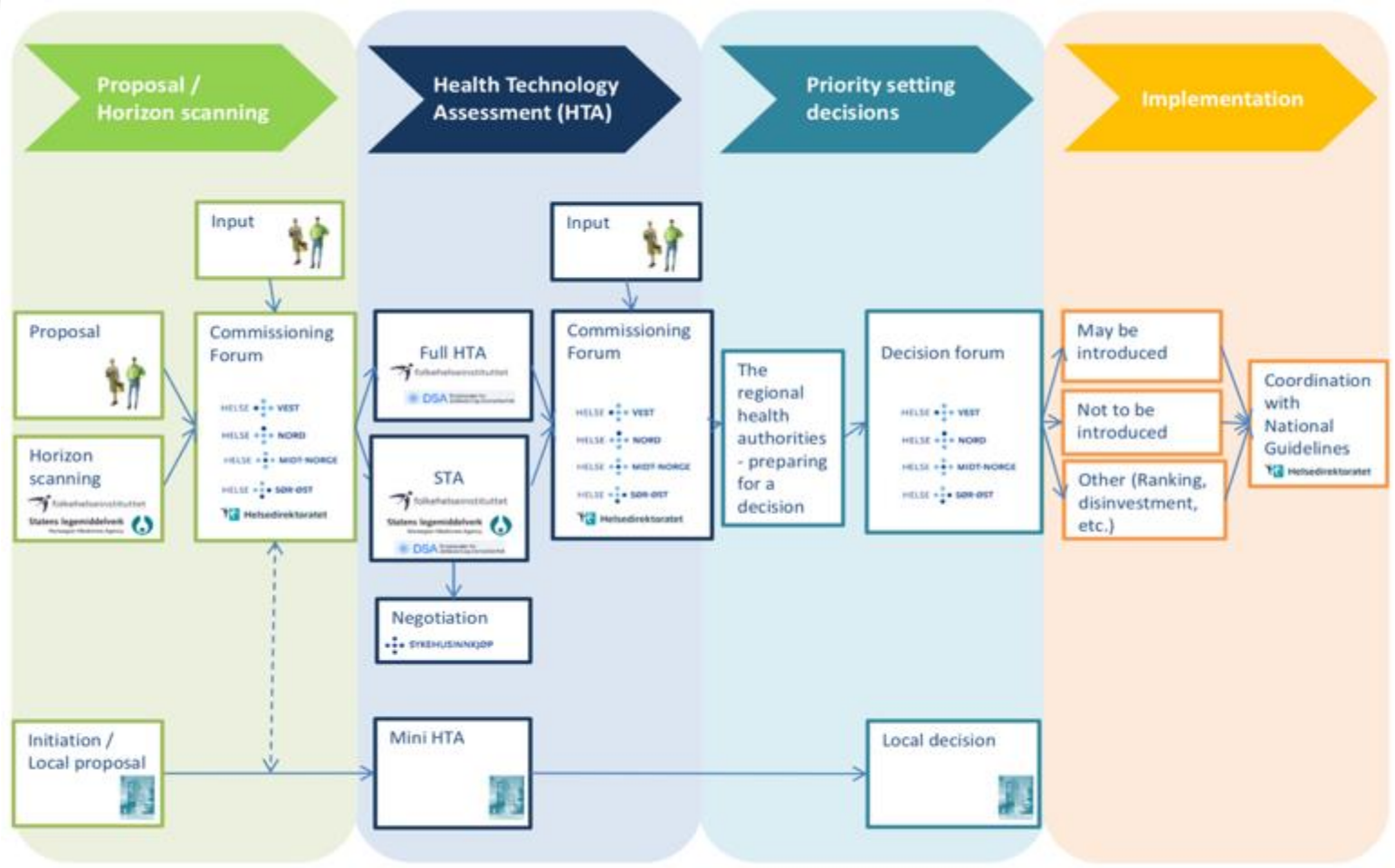
- Norway uses a health economic evaluation which takes a societal perspective with indirect costs of treatment and illness into account.
- There are three HTAs formats in Norway; mini-HTA, STA (Single Technology Assessment) and full HTA.
  - The mini-HTAs are limited assessments performed by clinicians and supporting units within the hospitals.
  - The STAs focus on a single mode of health technology related to a comparator and are performed by either the Norwegian Medicines Agency (if the mode is a medicine) or the Norwegian Institute of Public Health (all other mode).
  - Full HTAs are broad assessments performed at the national level by the Norwegian Institute of Public Health. The full HTAs may for example be used to compare various methods that have been used in clinical practice for some time.
- When performing Full HTA assessments, the Norwegian Medicines Agency or the Norwegian Institute of Public Health works in close dialogue with clinicians that, among others, have been recruited by the four regional health authorities.

Norway – HTA pathway

An overview of the national system for managed introduction of new health technologies within the specialist service in Norway processes.

The map is not solely for ATMPs, but for all new health technologies in the specialist health care services.

The objective is to ensure that new technologies meet health needs and sustainability. Of the health care system, managed introduction and prioritization offer important tools.



Norway – About NIPH

NIPH – Norwegian Institute of Public Health

- Norway's national public health institute is subordinate to the Ministry of Health and Care Services. NIPH acts as a national competence institution in public health in a broad sense for governmental authorities, the health service, the judiciary, prosecuting authorities, politicians, the media and the general public, international organizations and foreign governments.
- The Norwegian Institute of Public Health contributes to national and international Health Technology Assessments and performs the Full HTAs, pharmaceutical STAs and support mini-HTAs.

Mission

- To support decision makers in the health and welfare services by providing knowledge to help ensure high quality and equitable services.

Current activities of NIPH are divided into three main entities:

- HTA, systematic reviews and dissemination, teaching and support for EBM (Evidence-based Medicine) and evidence-based policy, clinical guidelines, The Grading of Recommendations Assessment, Development and Evaluation (GRADE) research and method development, method support to Cochrane, EPOC (Effective Practice and Organisation of Care Group) satellite, and secretariat for the Campbell Collaboration.
- Patient and user experience surveys, quality measurements and improvement in the health services, patient safety, and comparative health system analysis.
- Use of Norwegian electronic health library (Helsebiblioteket).

Norway – case example

- Imlygica drug developed by Amgen is reimbursed in Norway since 2017
- The product is a cancer medicine used to treat adults with melanoma. The overall efficacy and safety of Imlygic for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a)
- Approximately 15 adult patients are potentially suitable for the treatment of unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease each year in Norway.
- Budget impact calculations are uncertain and simplified. The budget impact of Imlygic will be relatively limited. A national centre for the treatment of suitable patient with T-vec can possibly limit even further the budget impact.

Denmark

Denmark: executive summary

- Denmark uses decentralized approach to HTA and reimbursement issues
- New independent council: “Medicinrådet”
- No nationwide regulation for sales prices, no new type of pricing model for ATMPs
- Use of HTA in policy decisions, planning, or administrative procedures is not required via regulations.
- Time-consuming HTAs difficult to reconcile with short-term political processes.

Denmark - Overview

National HTA organization	Danish Medicines Agency (DKMA) / *Medicinrådet*
Purposes of HTA	Clinical practice guidelines and protocols, Planning and budgeting, Pricing of health products, Indicators of quality of care
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Kymriah	GTMP	Not recommended as a standard treatment for relapses or refractory diffuse large-cell B-cell lymphoma after several systemic treatments. Recommended as standard treatment for B-cell acute lymphatic leukemia (ALL) who are refractory, in relapses following stem cell transplantation or in other or subsequent relapses.	No advanced payment method
Yescarta	GTMP	Not recommended as standard treatment for adult patients with relapses or refractory diffuse large-cell B-cell lymphoma after several systemic treatments.	No advanced payment method
Luxturna	GTMP	The Board of Medicines does not recommend the use of neparvovec as standard treatment for patients with hereditary RPE65-related retinal dystrophy.	No advanced payment method
Alofisel	sCTMP	Not recommended as possible standard treatment for Chron's Disease for some populations.	No advanced payment method
Holoclar	TEP	Recommended for some patient groups and not recommended for others.	No advanced payment method

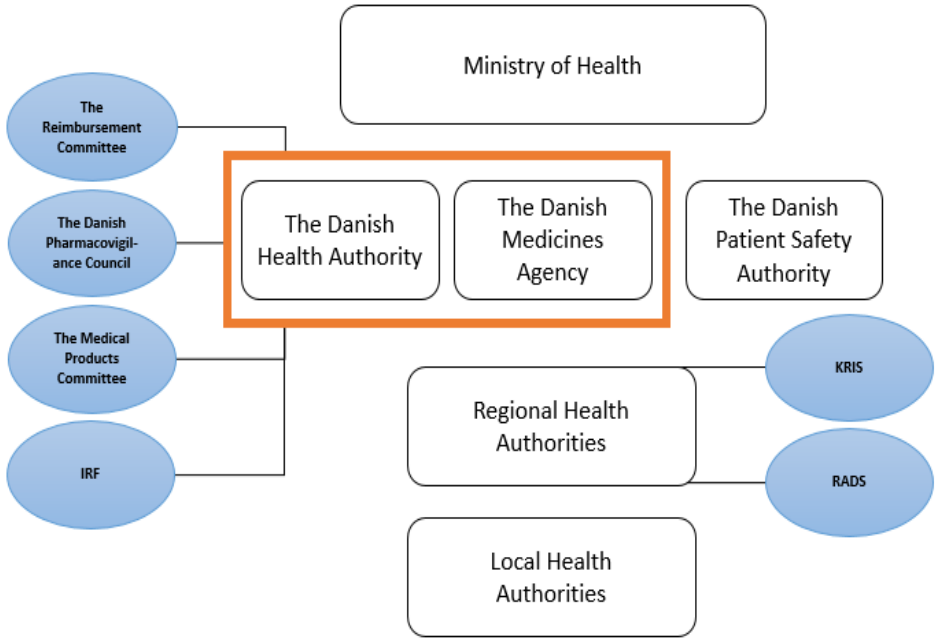
Denmark – Pricing and HTA methodology

Pricing

- Pharmaceutical companies do not have to apply for permission to set price for their medicines, there is no nationwide regulation for sales prices.
- Denmark, Norway and Iceland have started working together to negotiate prices on expensive pharmaceuticals.
- **We have not identified any new type of pricing model for approved ATMPs.**

HTA methodology

- Denmark is in the process of reorganizing its HTA system through the new independent council Medicinrådet. In recent years, it has been is decentralized after The Danish Centre for Health Technology Assessment department in the Danish Health and Medicines Agency closed in 2011.
- There is no regulatory mechanism in the Danish health service requiring the use of HTA in policy decisions, planning, or administrative procedures. Conclusions of HTA are often disregarded due to political or a health professional's priorities.
- A major concern about HTA is that the assessments are time consuming and thorough tasks. This can be difficult to fit into a short-term political process which often demands quick decisions



Denmark: case example

- Luxturna, a gene therapy developed by Kite/Novartis
- Approved by EMA since November 2018
- Luxturna (orphan drug) is approved for the treatment of eye disease hereditary RPE65-related retinal dystrophy
- Even though the clinical outcomes were positive, reimbursement was rejected due to its pricing (>600.000 EUR)

” It is sad that we cannot recommend a drug that is judged to have important added value, because the price is very high, says Steen Werner Hansen and Jørgen Schøler Kristensen”

Finland

Finland: executive summary

- Finland uses a centralized approach to HTA and reimbursement issues
- Currently no specific pathway for ATMP available
- Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)
- Rapid assessment is available
- Wealthy country, relatively strong purchasing power and available budget

Finland - Overview

National HTA organization	Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)
Purposes of HTA	Clinical practice guidelines and protocols, planning and budgeting, reimbursement/package of benefits
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Imlygic	GTMP	Recommended by quick mini-HTA	No advanced payment method - Fixed list prices
Kymriah	GTMP	Recommended (not by HTA)	No advanced payment method - Fixed list price of €330,000
Yescarta	GTMP	Recommended (not by HTA)	No advanced payment method -Fixed list price of €330,000
Alofisel	sCTMP	Recommended by quick mini-HTA	No advanced payment method -Not found

Finland – Pricing and HTA methodology

Pricing

- By 1st June 2019, 29 conditional reimbursement agreements have been made, 24 of which are in force. Cost-related uncertainties have been shared between a pharmaceutical company and society.
- Both the pharmaceuticals pricing board and the pharmaceutical companies have taken a favorable view of conditional reimbursements. However, a legislative change is required for its continuation.
- None of the conditional reimbursement agreements are used for ATMPs yet.

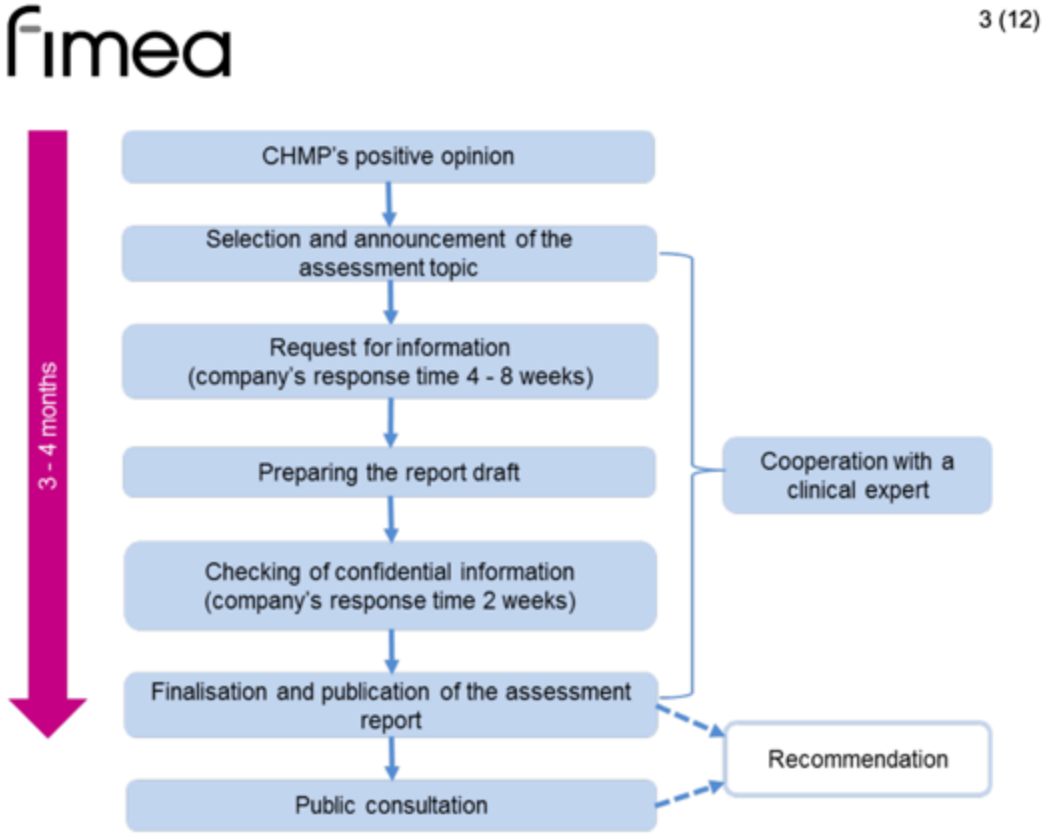
HTA is performed by FinCCHTA

- FinCCHTA, established in 2018, continues HTA activities previously carried out by the National Institute for Health and Welfare's department FinOHTA. Finland closely follows EUnetHTA approaches.
- FinCCHTA participates in the international HTA collaboration, health services and HTA research including distribution and organization of the hospital-based HTA work within the national HTA-network (five university hospitals jointly producing the reviews). FinCCHTA collects all jointly produced reviews and gives national recommendations based on this work. FinCCHTA also produces systematic reviews and original research papers.
- FinCCHTA is a permanent member (one seat) in the Council for Choices in Health Care in Finland (COHERE), which issues recommendations on services that should be included in the range of public health services in Finland. The Council works in conjunction with the Ministry of Social Affairs and Health. COHERE can order HTA reports from FinCCHTA or redirect themes proposed to it to FinCCHTA.
- FinCCHTA is active in teaching and knowledge dissemination in HTA and research methodology.

Finland – HTA assessement

RAPID ASSESSMENT OF NEW HOSPITAL-ONLY MEDICINAL PRODUCTS

- Assessment process A flowchart of the progress of the assessment process is presented in the figure below (CHMP = Committee for Medicinal Products for Human Use).



Source: FIMEA

Germany

Germany: executive summary

- Centralized system
- GBA is in charge of reimbursement decision in Germany
- HTA / Health Economics is a mandatory part of the reimbursement process
- Orphan ATMPs benefit from special regulations where they are granted additional benef

Germany - Overview

National HTA organization	Federal Joint Committee/ Gemeinsamer Bundesausschuss
Purposes of HTA	Pricing of health products, reimbursement/package of benefits
How HTA is used in decision-making	Mandatory, decision makers rely completely on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Glybera	GTMP	Non-quantifiable added benefit	Withdrawn from market
Imlygic	GTMP	No added benefit	Handled as procedure - not AMNOG assessed (The Arzneimittelmarkt-Neuordnungsgesetz)
Kymriah	GTMP	Non-quantifiable added benefit	Pay-for-performance
Yescarta	GTMP	Non-quantifiable added benefit	Pay-for-performance, G-BA assessed
Luxturna	GTMP	On-going G-BA assessment	-
Provenge	sCTMP	Non-quantifiable added benefit	Withdrawn from market
Zalmoxis	sCTMP	Non-quantifiable added benefit	GKV reimburses with € 130 000/infusion
Alofisel	sCTMP	Non-quantifiable added benefit	Currently under price negotiation
Chrondocelect	sCTMP	Not eligible to early benefit assessment	Withdrawn from market
Holoclar	TEP	Not eligible to early benefit assessment	Not assessed; not reimbursed

Germany – Pricing

Pricing

- **Prices for ATMPs are negotiated at a national level**. Discount agreements are possible to reach since developers are free to conclude them with individual health insurers or associations of health insurance funds. These can include risk-sharing agreements and capitation agreements.
- Example: health insurance service company IGQW signed a pay for performance risk-sharing agreement with Novartis for Kymriah, where Novartis will partially pay back the cost if the patient dies of his/her blood cancer within a defined period after the treatment.
- Budget impact and affordability: Germany uses a two-step assessment where the HTA assessment is the first step and the second is a price negotiations with payers who have made an independent assessment. Rebates are common for new drugs as opposed to outcomes-based agreements, which are rare.
- **Germany has implemented pay-for-performance for some of the approved ATMPs, G-BA assessed (The Federal Joint Committee: 'G-BA' (Gemeinsamer Bundesausschuss).**

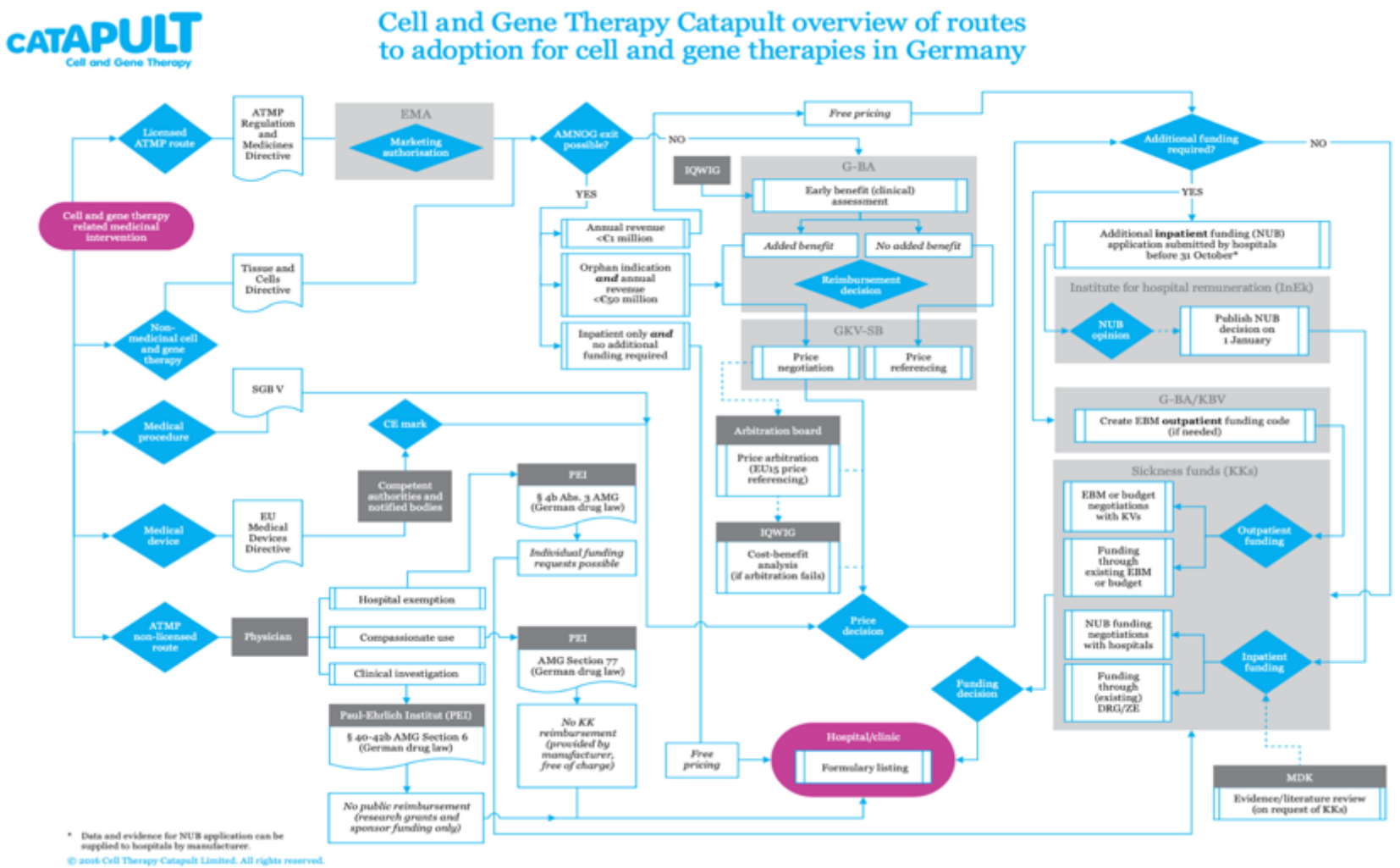
Germany- HTA stakeholders

- **The Ministry of Health: (Bundesministerium fuer Gesundheit) sets the framework for health care interventions**, approves measures taken within this framework, monitors the outcome of reforms and controls the work of the Statutory Sickness Funds. It is also the final decision-maker concerning reference pricing groups and reimbursement.
- **Federal Institute for Drugs and Medical Devices** (Bundesinstitut für Arzneimittel und Medizinische Produkte - BfArM) is an independent higher federal authority within the portfolio of the Federal Ministry of Health. One of the main tasks of the BfArM is the **authorization of finished medicinal products** on the basis of the German Medicines Act.
- The **German Institute for Health Technology Assessment: DAHTA** produces reports on medical, economic, social, ethical and legal issues related to the German health system, along with administering a database containing its own HTA reports, as well as national and international reports produced by other organizations. It provides information to interest groups and, together with scientific institutes, is involved in developing standards.
- **The Federal Joint Committee: 'G-BA' (Gemeinsamer Bundesausschuss**) is comprised of doctors, dentists, hospital representatives, representatives of the SHIs and patient representatives. The G-BA is the **central decision-making body concerning drug provision for those with statutory health insurance**. It regulates reimbursement and restrictions on prescribing on efficiency grounds. Furthermore G-BA assesses new methods of medical examination and treatment, evaluates and classifies new drugs on the German market and is responsible for the publication of treatment guidelines (submitted for approval to the Federal Ministry of Health).

Other HTA-related findings for Germany

- Orphan ATMPs benefit from special regulations where they are granted additional benefit, of relative lower burden of evidence compared to other medicines, by law if the annual sales do not exceed €50M.
- Extrapolation of data from new kinds of evidence than the traditional randomized controlled trials are frowned upon which makes it challenging to recognize and quantify long-term costs or potential outcome benefits.
- Germany have reimbursed six ATMPs, of which four is still on the market.

Germany- HTA Process



Germany: case example

- Kymriah manufactured by Novartis
- CAR T-cell therapy for patients 25 or younger with refractory and acute lymphocytic B-cell leukaemia, and for adults with relapsed/refractory diffuse large B-cell lymphoma.
- In order to ensure patient access to treatment, a group of German health insurance providers (GWQ; Gesellschaft für Wirtschaftlichkeit und Qualität für Krankenkassen) has offered Novartis an outcome-based deal, something almost unheard of in Germany.
- GWQ will fund their patients for Kymriah, to the price of €320,000. If the patient dies of the disease before a specific time point, Novartis will partially reimburse these costs.

Netherlands

Netherlands: executive summary

- Centralized decision making process
- Focus on HTA and health economic models in all decision making. Highly price sensitive.
- Long established history of HTA and health economics, with leading institutions and academics
- Known to be one of the more ‘pushy’ countries when it comes to negotiations with pharmaceutical companies regarding price

Netherlands - Overview

National HTA organization	The National Health Care Institute/ Zorginstituut Nederland (ZINL)
Purposes of HTA	Reimbursement/ package of benefits
How HTA is used in decision-making	Results of HTAs have to be considered in decision-making process

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Strimvelis	GTMP	Reimbursed as orphan drug	No advanced payment method
Yescarta	GTMP	Put in ”waiting room” for expensive drugs	No advanced payment method
Holoclar	TEP	Reimbursed as orphan drug	No advanced payment method

The Netherlands – Pricing & HTA

Pricing

- New pricing project is being tried, the "no cure, no pay" model. Certain expensive cancer drugs will be paid for only if they turn out to be effective after 16 weeks. However, **none of the ATMPs approved by EMA are under this scheme.**
- Netherlands are part of the joint initiative BeNeLuxAI, a collaboration between the governments of Belgium, The Netherlands, Luxembourg, Austria and Ireland. Aim: to ensure sustainable access to innovative medicine at affordable cost for patients.

HTA - methodology

- The National Health Care Institute (Zorginstituut Nederland, ZIN) conducts the HTA of pharmaceutical products, makes recommendations for reimbursement in order to manage the basic health care package and to ensure that it contains all necessary care
- Whether pharmaceuticals are part of the basic package is assessed on the basis of our four package criteria: necessity, effectiveness, cost-effectiveness and feasibility.
- HTA process usually starts with a request from the manufacturer. Before the official dossier is submitted, a draft dossier is often discussed. From the submission of a complete final dossier to the reimbursement decision it usually takes 90 days for outpatient drugs and 4 months for hospital drugs. Experts from ZINL write a report that is submitted for advice to the scientific advisory board (WAR). Thereafter, the Board of the ZINL sends a recommendation on reimbursement to the Minister of Health, Welfare and Sport (VWS) which makes the final reimbursement decision. Pharmaceutical products dispensed in community pharmacies are always assessed, hospital drugs are assessed if they have a major budget impact. The ZINL can also make a statement whether a care intervention, including pharmaceutical products, should be reimbursed by national insurance companies in a so-called position paper (guiding).

The Netherlands – Stakeholders

- Before a drug can be introduced into the market, it must be authorized by the **Medicines Evaluation Board** (College ter beoordeling van Geneesmiddelen) (MEB). The MEB is part of the Ministry of Health, Welfare and Sport.
- The MEB evaluates the drug based on criteria cited in the Medicines Act 2007 (Geneesmiddelenwet) and sets the conditions for authorizing the product for marketing in The Netherlands. The responsibility for the evaluation, authorization and pharmacovigilance of medicinal products for human use (including homeopathic and herbal medicines) rests with the MEB, which consists of doctors, pharmacists and scientists. The MEB has independent authority to take decisions on the availability of these medicinal products. The MEB is responsible for both the authorization and monitoring of effective and safe medicinal products and is jointly responsible for the approval of the medicinal products throughout the EU.

The Netherland – case example

- Holoclar, produced by Chiesi, received EMA approval in 2014
- Stem-cell treatment used in the eye to replace damaged cells on surface (epithelium) of the cornea, the transparent layer in front of the eye covering the iris. Used in adult patients with moderate to severe limbal stem-cell deficiency
- List price of € 81750,00

United Kingdom

United Kingdom: executive summary

- Centralized decision making process
- Big focus on patient access schemes
- Only applicable for England and Wales
- Budgetary planning in the UK health service is not set up for potentially curative one-time therapies, such as gene therapies.

United Kingdom - Overview

National HTA organization	National Institute for Health and Care Excellence
Purposes of HTA	Clinical practice guidelines and protocols, Planning and budgeting, Indicators of quality of care
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Imlygic	GTMP	Recommended with restriction	Patient access scheme
Strimvelis	GTMP	Gained full recommendation within its marketing authorisation via NICE's Highly Specialised Technology process	Patient access scheme
Kymriah	GTMP	Recommended by NICE	Reimbursed via Cancer Drugs Fund
Yescarta	GTMP	Recommended by NICE	Reimbursed via Cancer Drugs Fund
Luxturna	GTMP	Recommended by NICE	Patient access scheme, limited number of patients
Provenge	GTMP	Not recommended	Withdrawn from market
Alofisel	sCTMP	Not recommended	Not recommended
Chondrocelect	sCTMP	Recommended	Withdrawn from market
MACI	TEP	Recommended	Withdrawn from market
Holoclar	TEP	Recommended with restriction by NICE	Patient access scheme
Spherox	TEP	Recommended	Patient access scheme

United Kingdom – Pricing

Pricing

- 7 out of 10 ATMP drugs are reimbursed to date. Only one of these, Strimvelis®, was reimbursed at its full list price.
- Budgetary planning in the UK health service is not set up for potentially curative one-time therapies, such as gene therapies.
- In UK, Patient Access Schemes (PAS) are routinely used. Mostly, they are confidential discounts and in rare cases, they are outcome-based agreements.
- The UK uses fund-based payment models. An example of this is the Cancer Drugs Fund which can pay for new cancer drug even if they can be rejected by NICE.
- The UK information excludes Scotland as they have their own HTA system.

United Kingdom – HTA Stakeholders and methodology

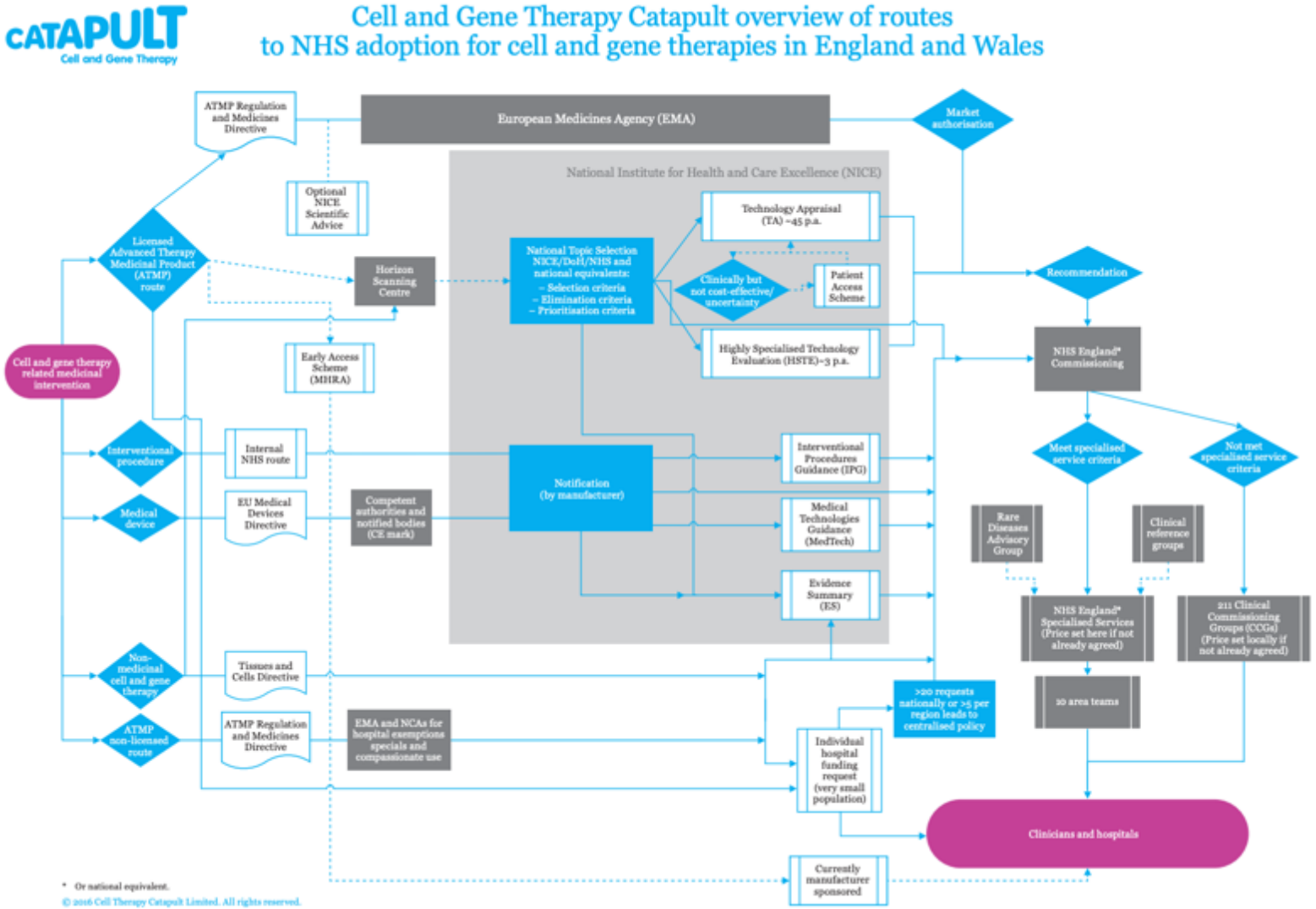
NICE – National Institute for Health and Care Excellence

- Set up in 1999 to reduce variation in the availability and quality of NHS treatments and care; began developing public health guidance in 2005.
- NICE's role is to improve outcomes for people using the NHS and other public health and social care services.
    - Producing evidence-based guidance and advice for health, public health and social care practitioners.
    - Developing quality standards and performance metrics for those providing and commissioning health, public health and social care services.
    - Providing a range of information services for commissioners, practitioners and managers across the spectrum of health
    - The health economic evaluation in UK has a health system perspective where only direct costs to the health care system are considered as opposed to taking indirect costs of treatment and illnesses into account as well.

HTA Nice – appraising health technologies via two routes:

- Multiple Technology Appraisal (MTA): examine a disease area or class of drugs and contain either new evidence gathered after the launch of a drug or include new economic modelling. The MTA process is based on input from a broad range of stakeholders, with emphasis on the Assessment Group who critically reviews the available evidence and produces an Assessment Report.
- Single Technology Appraisal (STA): STAs have been developed to provide early guidance for new drugs targeting a single indication, as well as for new indications for drugs already on the market. This process has been developed to reduce the effect of NICE blight and drugs thought to improve life expectancy are likely to be prioritized. This process is more streamlined that the MTA process, with greater emphasis on the submission of evidence from the manufacturer. STA allows products which show plausible cost-effectiveness to enter into a Managed Access Agreement (MAA), whereby a restricted set of patients gain access to a treatment whilst more evidence is generated.

United Kingdom - HTA Process



United Kingdom– case example

- Strimvelis, produced by Orchard Therapeutics (ex-GSK), received EMA approval in 2016
- Aimed at ultra-rare disease, Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID), with about 15 patients annually in Europe
- Treatment is individualized and the only manufacturing facility is in Milan. The product's shelf-life is about 6 hours.
- UK based patients will therefore need to travel to Milan in order to be eligible for treatment, for now the NHS cover this, pending Brexit.
- Product is reimbursed and priced at around 594 000 EUR, making it one of the more expensive product available globally. However it does promise a cure, as opposed to ongoing longer-term treatment e.g. it's a one-off cost
- Current reimbursement condition includes a money-back guarantee in case the treatment is not successfull.
- Clinical trial data showed 100% overall survival and 100% event free survival at 24 months, demonstrating favorable outcomes compared to a historical control group of patients

Orchard therapeutics

France

France: executive summary

- France uses a centralized approach to HTA and reimbursement issues
- There are not official ATMP pathways but since many ATMPS are also orphan drugs and generally have a high unmet need they can benefit from emporary authorization for use (ATU), early access for compassionate use.
- Haute Autorité de Santé (HAS) is key decision maker

France- Overview

National HTA organization	Haute Autorité de Santé (HAS), Commission d'Evaluation des Médicaments, Agence Française de Securité Sanitaire des Produits de Santé (AFSSAPS), Transparency Commission (TC), Comité Economique des Produits de Santé (CEPS)
Purposes of HTA	Improve the quality of care delivered to patients
How HTA is used in decision-making	Usually clinical, in some cases health economic

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Glybera	GTMP	Not recommended	Withdrawn from market
Kymriah	GTMP	Recommended	Price in negotiation / available through post ATU program* (Temporary Authorization for Use)
Yescarta	GTMP	Recommended	Reimbursed: Price set at € 327.000 for one injection with efficacy conditions in real life
Luxturna	GTMP	Recommended	Price in negotiation / available through post ATU program* (Temporary Authorization for Use)
Zalmoxis	sCTMP	Not recommended	Negative reimbursement decision
Alofisel	sCTMP	Recommended	Price in negotiation / available through post ATU program* (Temporary Authorization for Use)
Chondrocelect	sCTMP	Not recommended	Withdrawn from market
Holoclar	TEP	Recommended with restriction	Positive reimbursement decision / funding by hospitals

* Early access compassionate use program

France– Pricing

Pricing

- Agreements of price-volume and rebates are routinely negotiated for new medicines in France. Payment-by-result are rare, and it is limited to drugs in areas of clinical need when evidence at launch is not sufficient by usual HTA standards.
- If Comité Economique des Produits de Santé (CEPS) does not reach a price agreement with the developer, any of the parties can propose an established conditional price while further post-marketing data is collected.
- For the budget impact and affordability, France uses a two-step assessment where the HTA assessment is the first step and the second is price negotiations with payers who have made an independent assessment.
- Some of the ATMP have received what is called a temporary authorization for use (ATU), early access for compassionate use.
- **We have not identified any new type of pricing model for approved the ATMPs.**

Other

- The French HTA bodies are highly driven by clinical evidence which makes them reluctant to provide access based on data available at the time of launch of an ATMP. Consequently, patients in need of therapy are not able to access new treatments in a timely manner. Two examples of this is with the cases of Glybera and Chondrocelect which were denied reimbursement in France due to uncertain clinical evidence.
- With the delayed reimbursement of a product as a background, collecting post-marketing evidence is very challenging for manufacturers.
- Four ATMPs have been recommended for reimbursement by French HTA bodies.

France– HTA stakeholders

HAS – Haute Autorité de Santé

- The Haute Autorité de santé (HAS), the French national authority for health, is a consultative body providing independent scientific advice to the French public authorities. It was formed by the merger of ANAES (French National Agency for Accreditation and Evaluation in Health), the Transparency Committee, and the Committee for the assessment of devices and health technologies (CEPP) and FOPIM (Fund for the Promotion of Medical and Health Economics Information). The objective was to bring together into a single body all the expertise needed for patient-centered continuous quality improvement.

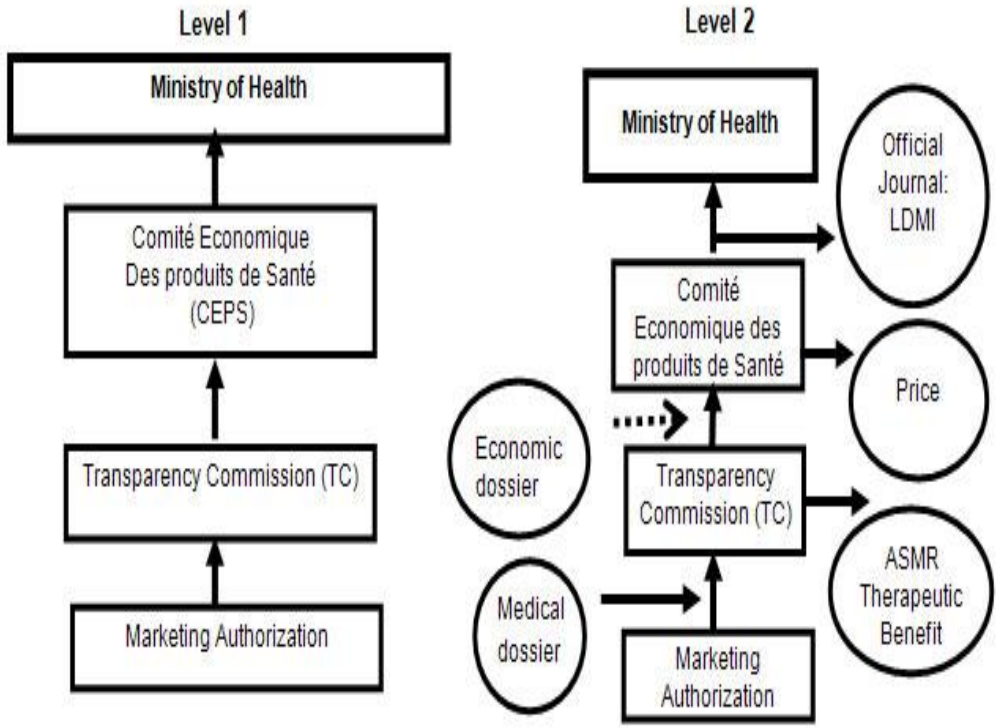
Mission

- HAS' mandate is to improve the quality of care delivered to patients through measures such as the production of good practice guidelines, the development of disease management programs for chronic conditions, continuing professional development (CPD), and accreditation of health care organizations.
- Practice appraisal becomes compulsory for all practitioners. HAS also assesses the expected and actual clinical benefit of drugs, medical devices, and diagnostic and therapeutic procedures and advises the authorities on their reimbursement. HAS will certify prescription software and compliance with the medical sales representatives' code of practice.
- HAS is governed by a board of eight members; the Board Chair is appointed by the Head of State. HAS may perform assessments on its own initiative or at the request of government (eg the Ministry of Health), national health insurance, learned societies, users' associations, etc. There are seven specialist committees, each chaired by a Board member. Each Board member is responsible for the policy, strategy and executive powers of their committee, and sets up working groups. Each Chair is supported by an operational manager who reports to the Director of HAS.

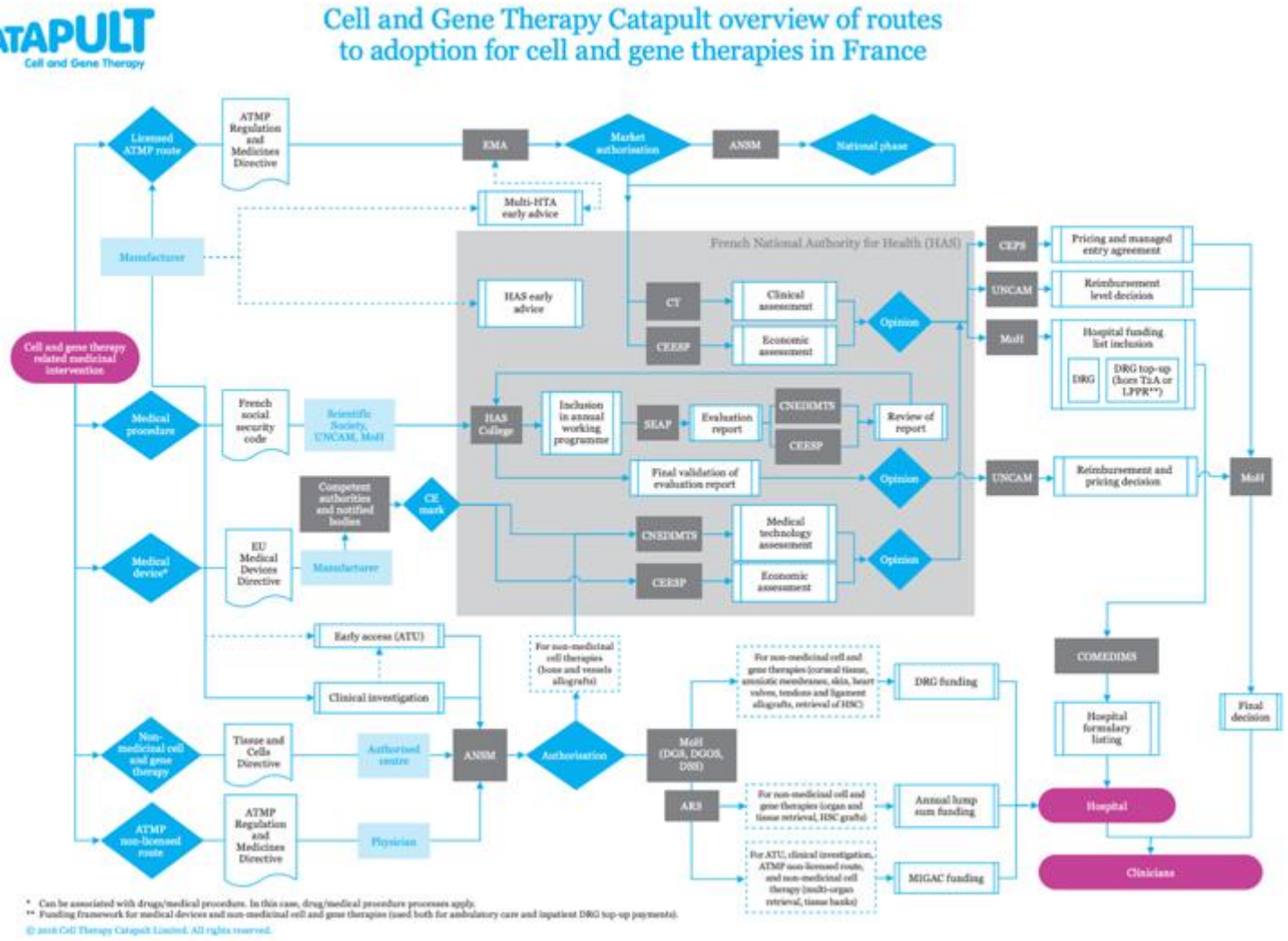
France – HTA methodology

DECISION-MAKING PROCESS

- The general conditions of the reimbursement system are established by law and implemented principally at national level by governmental bodies.
- When marketing authorization is granted either by the EMEA or the French Medicine Agency (AFSSAPS), the company has to apply for reimbursement on positive lists to obtain funding by the mandatory health insurance (*assurance maladie obligatoire*).
- The decision-making process can be found to the right. Decision-making bodies are represented in boxes and the solid arrows are required steps in the process.



France- HTA Process



France– case example

- Yescarta, produced by Gilead (ex-KITE), received EMA approval in 2018
- For treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL)
- In France, Yescarta received market access through the ATU system (The Temporary Authorisation for Use (ATU) which allows patients to benefit from pharmaceutical specialities whereas they do not have any marketing authorization, provided that they are intended for the treatment of serious or orphan diseases and in the absence of appropriate treatment.)
- Yescarta achieved a moderate added benefit rating in DLBCL, despite the lack of direct comparison and long-term efficacy data, and evidence of significant short-term toxicity and lack of longer-term safety data.
- The list price in France was set at 327 000 EUR
- Currently 5> approved centers in France

Spain

Spain: executive summary

- Decentralized system
- Many reimbursement decisions are made regionally which often causes the budget impact to outweigh other considerations in the evaluation of ATMPs.
- Current legislation makes annuity payments impossible since committing for long-term spending for drugs is not allowed.

Spain Overview

National HTA organization	Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System
Purposes of HTA	Clinical practice guidelines and protocols, planning and budgeting, pricing of health products, indicators of quality of care, reimbursement/package of benefits
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Imlygic	GTMP	Not found	Authorized, not commercialized yet
Kymriah	GTMP	Not found	Reimbursed; payment by results
Yescarta	GTMP	Not found	Reimbursed; payment by results
Chondrocelect	sCTMP	Recommended	Withdrawn from market
Alofisel	sCTMP	Not found	Reimbursed; payment by results
Holoclar	TEP	Not found	Commercialized, but not reimbursed

France– Pricing & Reimbursement

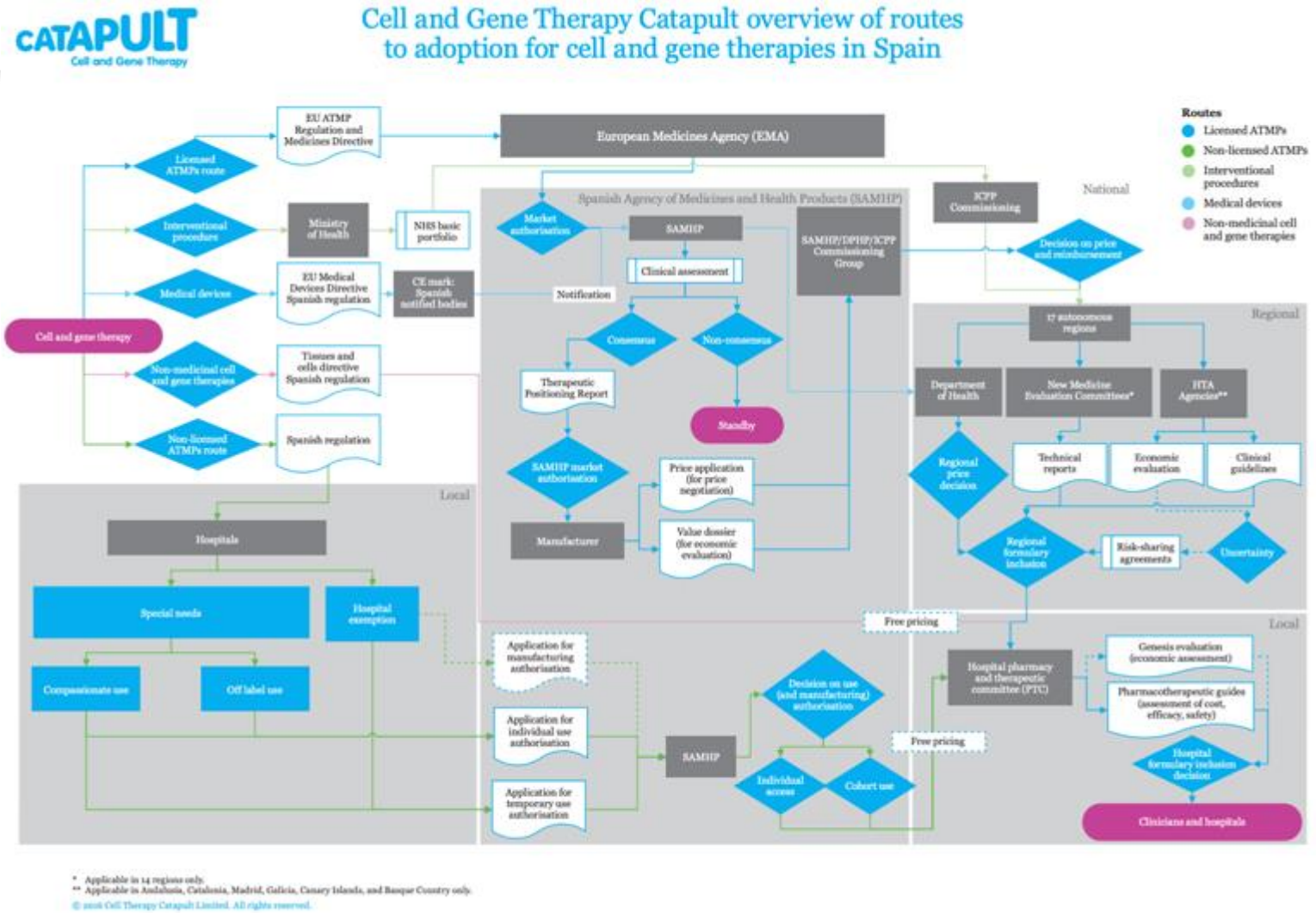
Pricing and reimbursement

- Three therapies are reimbursed (Kymriah®, Yescarta® and Alofisel®; all of them with a payment by results agreement), one is commercialised but not reimbursed (Holoclar®); and the others are not commercialized. The three therapies that are reimbursed have been evaluated using Valtermed.
- When marketing authorization is granted either by the European Medicines Agency (EMEA) or the Spanish Medicine Agency AEMPS (Agencia Espanola del Medicamento y Productos Sanitarios), the Ministry of Health (MSC) initiates a procedure to decide on reimbursement of this new product on the national reimbursement list. The manufacturer is then invited to provide all relevant information to allow the Inter-Ministerial Pricing Commission CIPM (La Comisión Interministerial de Precios de los Medicamentos), led by MSC, to make a decision. If the outcome is positive (inclusion in the national reimbursement list), this decision is valid (mandatory) throughout the country.
- Many reimbursement decisions are made regionally which often causes the budget impact to outweigh other considerations in the evaluation of ATMPs.
- The view of pricing in Spain is that outcomes-based agreements, as well as expenditure cap agreements, can be reached between both the national and regional authorities with the pharmaceutical companies.
- Current legislation makes annuity payments impossible since committing for long-term spending for drugs is not allowed.
- **Spain has implemented new payment method, based on results.**

France– HTA & Reimbursement

- The National Health Service SNS (Sistema Nacional de la Salud) provides healthcare to the Spanish population. It is coordinated and supervised by the Ministry of Health and Consumer Affairs MSC (Ministerio de Sanidad y Consumo). Since the decentralization of healthcare to the seventeen autonomous regions (Comunidades Autónomas), the MSC focus more on pharmacovigilance, product approvals, cost-containment and long-term policies. The regions are responsible for the healthcare delivery and financing of it.
- **There are three different HTA levels in the country**:
  - national level for common benefit package excluding pharmaceuticals,
  - national level for pharmaceuticals, and
  - regional level.
- The HTA must include information about cost, efficacy, efficiency, effectiveness, safety and health care utility of the technology. The proposal of inclusion of new technologies that could significantly increase health expenditures also requires approval by the Fiscal and Financial Policy Council (Consejo de Politica Fiscal y Financiera Financial).
- The HTA for pharmaceuticals has a different process than that the HTA of other health care technologies.
- Due to the lack of either tools to cope with uncertainty in HTAs for ATMPs or experience and expertise, Spain as delayed ATMP assessments. This creates a problem with the time to access for patients in need of ATMPs.
- Access to gene therapy must follow the guidelines established in the “PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR”, included in it are besides other aspects:
- A network of reference centers for the use and administration of CAR-T therapies is being developed in Spain. Conditions are to be fulfilled by the centers for manufacturing CAR-T in Spain.

Spain HTA Process



Spain– case example

- Alofisel, produced by Takeda (ex-TiGenix) received EMA approval in 2018 and classified as an orphan drug
- Used to treat complex anal fistulas in adults with Crohn's disease

- Alofisel is created out of mesenchymal stem cells derived from the fat tissue of a donor. Specific cells are cultivated in a laboratory setting and subsequently injected intop the fistula walls. With the aim to lower inflammation and promote tissue regeneration and growth which in turn allows fistulas to close up.
- Phase II trial with over 200 patients, showing 50% of patients closed all their fistulas with a single dose of Alofisel and 42% more efficiacy as compared to normal Crohn's treatment (infliximab + immunomoluators).
- Reimbursements in Spain and several other countries are based on value-based pricing, i.e., certain conditions need to be met. The MAH needs to reimburse part or all of the cost of the drug if patients using it do not see improvement. Current price of the product is between 50 and 60 000 EUR.

Italy

Italy: executive summary

- Budget impact is one of the decision criterion for HTAs in Italy.
- In Italy, the general conditions of the reimbursement system are established on a national level and implemented at a regional level by governmental bodies.
- Italy uses MEAs (Managed Entry Agreements), which have ensured faster ATMP assessments and market access than other countries in in the EU.

Italy - Overview

National HTA organization	Italian Medicines Agency (AIFA) and national Agency for regional health services (AGENAS)
Purposes of HTA	Planning and budgeting, pricing of health products
How HTA is used in decision-making	Advisory, decision makers rely partly on the advice

HTA reviewed approved ATMP

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Imlygic	GTMP	List Cnn: Not yet assessed	Not commercialized
Kymriah	GTMP	Information not found	Payment by results (ALL); obligatory discount (DLBCL)
Strimvelis	GTMP	List H: Hospital only	Reimbursed; payment by results
Zalmoxis	sCTMP	List H: Hospital only	Reimbursed; flat price per patient
Holoclar	TEP	List H: Hospital only	Reimbursed; payment by results

Italy – Pricing

Pricing

- Budget impact is one of the decision criterion for HTAs in Italy.
- Italy uses MEAs (Managed Entry Agreements), which have ensured faster ATMP assessments and market access than other countries in in the EU. These MEAs are used to control the spending on expensive and innovative products and take either of the three forms payment by results, cost-sharing or risk-sharing.
- Kymriah, Strimvelis and Holoclar are currently available under a payment-by-result scheme or what is also called Managed entry agreements. Salmoxis has a flat cost per patient no matter of dosage.

Reimbursement

- In Italy, the general conditions of the reimbursement system are established on a national level and implemented at a regional level by governmental bodies.
- When marketing authorization is granted either by the European Medicines Agency (EMEA) or the Italian Medicine Agency AIFA (Agenzia Italiana del Farmaco), the company may apply for reimbursement on the National Pharmaceutical Formulary PFN (Prontuario Farmaceutico Nazionale). A product can be assigned to Class A, H or C.
    - Class A includes essential products and those intended for chronic diseases and are fully reimbursed by the national healthcare system.
    - Class H includes products that are only fully reimbursed in the hospital
    - Class C includes other products which do not have the characteristics of Class A and are not reimbursed.
- Drugs that get the classification innovative may be paid by a separate fund and then be exempted from traditional budget caps and subsequently be included in regional formularies.
- Reimbursement decisions often are made regionally which often causes the budget impact to outweigh other considerations in the evaluation of ATMPs.

Italy – HTA stakeholders

The National Healthcare System SSN (Servizio Sanitario Nazionale) provides healthcare coverage to the Italian population. Although it is under the responsibility of the Ministry of Health, the system is decentralized resulting in three levels:

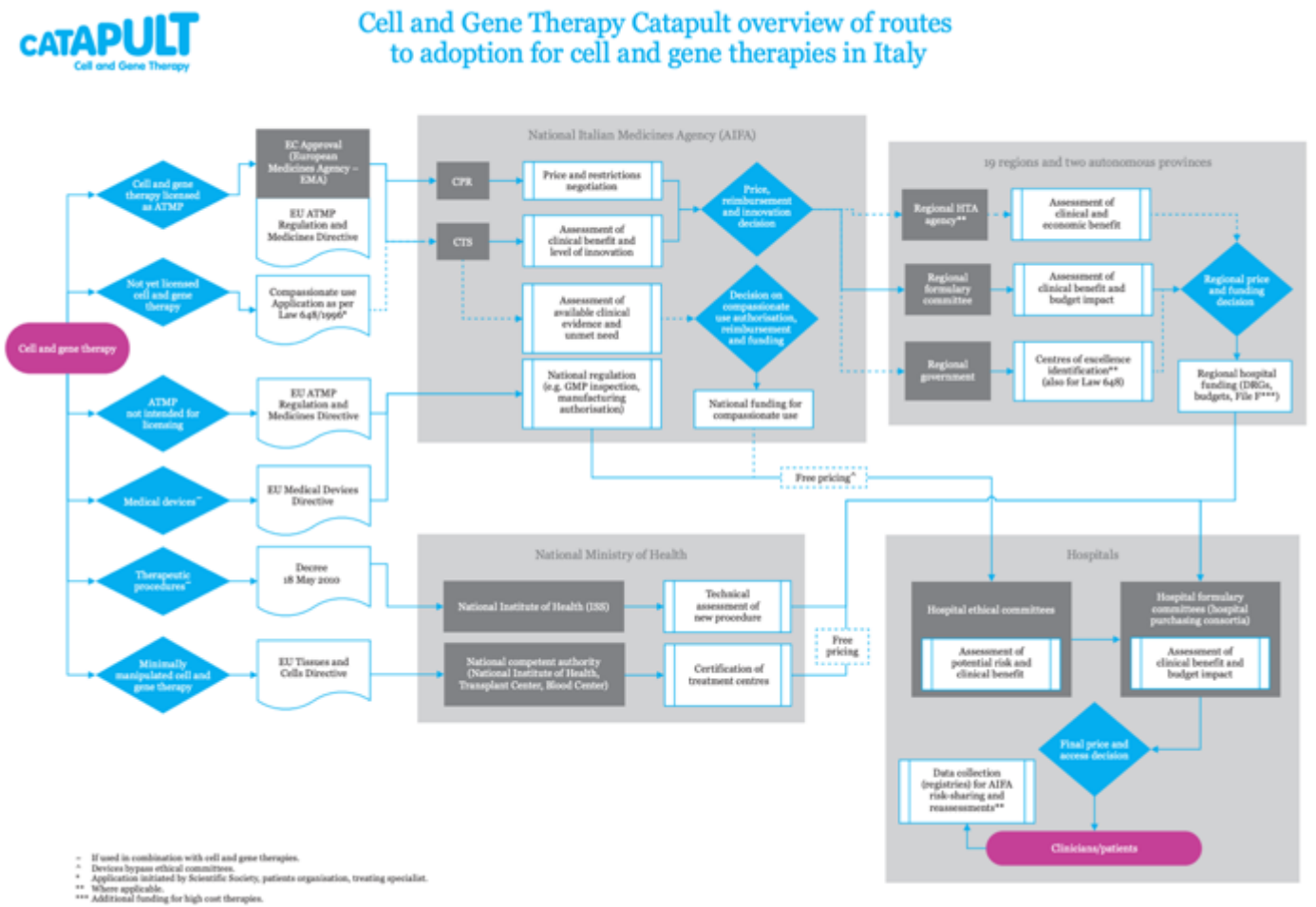
- National level: The Ministry of Health formulates every three years a healthcare plan PSN (Piano Sanitario Nazionale) that determines healthcare policies.
- Regional level: Twenty regions implement the PSN with their own resources and can adjust to region-specific needs. As a consequence, geographic disparity in terms of healthcare access or the level of co-payments exists.
- Local level: Local health units ASL (Azienda Sanitaria Locale) provide the health care services – e.g. primary medical services, coordination of all non-emergency admissions to public hospitals.

Reimbursement Organizations/HTA Organizations

- AIFA (Agenzia Italiana del Farmaco)
  Within the Italian Medicines Agency (AIFA), two committees are involved in the pricing and reimbursement procedure for pharmaceuticals.
- CTS (Comitato Scientifico e Tecnico)
  This committee makes a decision on the reimbursement, local marketing authorization and positive list revisions.
- CPR (Comitato Prezzi e Rimborso) This body will assess the manufacturers applications, collect information from the National Observatory on the Use of Pharmaceuticals (OsMED) and will negotiate reimbursement with the manufacturers.

When AIFA considers a new drug, level of innovation, unmet need, added therapeutic benefit and evidence quality is considered. Orphan drugs are partly or fully exempted from the evidence quality criterion and new rules from 2017 are designed to faster and more streamlined access throughout the country.

Italy - HTA Process



Italy – case example

- Strimvelis, produced by Orchard Therapeutics (ex-GSK), received EMA approval in 2016
- Aimed at Ultra-rare diesease, Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID), with about 15 patients annually in Europe
- Treatment is individualized and the only manufacturing facility is in Milan. The product shelf-life is about 6 hours, so all patients have to travel to Milan for treatment.
- Product is reimbursed and priced at around 594 000 EUR, making it one of the more expensive product available globally. However, it does promise a cure, as opposed to ongoing longer-term treatment e.g. it's a one-off cost
- Current reimbursement condition includes a money-back guarantee in case the treatment is not successfull.
- Clinical trial data showed 100% overall survival and 100% event free survival at 24 months, demonstrating favorable outcomes compared to a historical control group of patients

Orchard therapeutics

North America

- Canada

- USA

Canada

Canada: executive summary

- Canada uses a centralized decision making process for its MA and reimbursement decisions (except Quebec)
- Special rapid process exists in Ontario only
- Canada uses a mix of both universal and private healthcare
- Health Canada is the federal health department and responsible for drug approval, safety and efficacy

Canada - Overview

National HTA organization	Health Canada, The Canadian Agency for Drugs and Technologies in Health
Purpose of HTA	To ensure prices are not excessive
How HTA is used in decision-making	In dossier evaluation

Reviewed ATMPs

Brand name	ATMP technology	HTA assessment of therapy	Payment method
Prochymal	sCTMP	Granted for acute graft-versus host disease in children	Approved in market but not reimbursed
Kymriah	GTMP	Positive, pending a rebate	Normal payment / coverage
Yescarta	GTMP	Positive	Normal payment / coverage

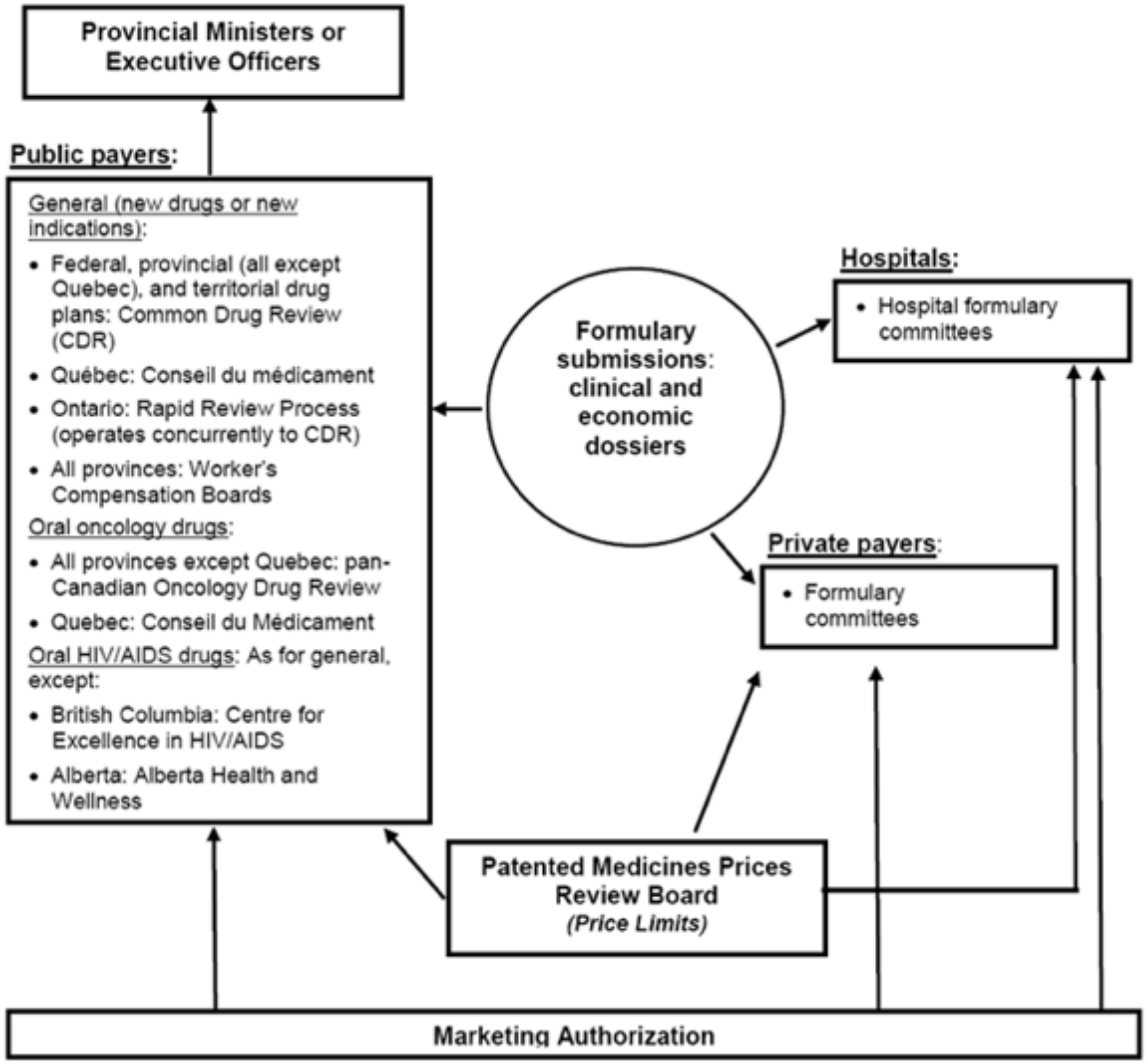
Canada HTA stakeholders

- **Health Canada** The federal health department is responsible for approving new drugs based on their safety and efficacy, among other factors. Health Canada releases a formal marketing and distribution authorization (Notice of Compliance [NOC]) if the new drug's profile conforms to the Food and Drugs Act and Regulations. Health Canada is also responsible for promoting healthy living to Canadians by communicating information on disease prevention, drug safety, and other health-related issues.
- **The Patented Medicine Prices Review Board (PMPRB)** The PMPRB is an independent body within the federal health portfolio, responsible for regulating drug prices for all prescription and non-prescription patented drugs sold in Canada. PMPRB submits to the federal parliament, through the Minister of Health, an annual report including analyses of patented drug prices, price trends, and research and development expenditures of patent-holding drug manufacturers.
- **The Canadian Agency for Drugs and Technologies in Health (CADTH)** CADTH is an independent, not-for-profit agency funded by federal, provincial, and territorial governments, to provide evidence-based information about the effectiveness of drugs and other health technologies to Canadian healthcare decisionmakers. CADTH fulfils its mandate through the Health Technology Assessment (HTA) program, the Common Drug Review (CDR; see below) process, and the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) which identifies and promotes optimal drug therapy.
- **The Common Drug Review (CDR)** Under CADTH's mandate, the CDR process accepts drug submissions from manufacturers, conducts systematic drug reviews, and provides participating public drug plans (federal, territorial, and all Canadian provinces except Québec) with evidence-based clinical and economic information, and expert advice, to support their formulary listing decisions.
- **pan-Canadian Oncology Drug Review Process (pCODR)** pCODR is a cross-jurisdictional review process for all oncology drugs, based on Ontario's existing cancer drug review. Participating provinces (Manitoba, Saskatchewan, British Columbia, Alberta, Nova Scotia, Newfoundland, Prince Edward Island, and New Brunswick) each make their own final funding decision based on input from the Committee to Evaluate Drugs (CED) and the CED-Cancer Care Ontario (CCO) Subcommittee.
- **Conseil du médicament – Québec** This provincial body accepts drug submissions from manufacturers and makes recommendations concerning listing a drug on the provincial drug formulary (Liste de medicaments). Final listing decision is made by Québec's Minister of Health.

Canada – Pricing

- Pricing of pharmaceuticals, including cell/gene therapies are managed through the federal government in cooperation with the Patented Medicine Prices Review Board which is an independent government body responsible for drug price regulation
- Outside the hospital setting, drugs are reimbursed to the majority of Canadians by private health insurance plans
- Data requirements are specific to each jurisdiction for which listing status is sought. However there are requirements that are common to all or most jurisdictions; these include:
  a) the price to be charged for all dosage forms
  b) product characteristics (from the Product Monograph)
  c) clinical efficacy and safety data
  e) economic evaluation
  f) budget impact assessment.

Canada HTA Process



USA

USA: executive summary

- The USA is the largest market for pharmaceuticals and related products in the world
- No universal health coverage but has Medicare and Medicaid
- Highest health expenditure globally
- Pharmaceutical prices are generally higher as compared to Europe
- FDA is responsible for Market Authorization with various public and private decision makers regarding pricing and reimbursement

USA- Overview

National HTA organization	FDA (national Food & Drug Administration), but not responsible for HTA
Purposes of HTA	No Federal HTA requirement, but Agency for Health Care Quality in cases uses HTA for Medicare program
How HTA is used in decision-making	Depends on situation, no formal process

Reviewed approved ATMPs

Brand name	ATMP technology	assessment of therapy	Payment method
Yescarta	GTMP	FDA market authorization	
Zolgensma	GTMP	FDA market authorization	
Provenge	sCTMP	FDA market authorization	
Luxturna	GTMP	FDA market authorization	
Kymriah	GTMP	FDA market authorization	
Imlygic	GTMP	FDA market authorization	

USA– Stakeholders

- The **Department of Health and Human Services (HHS)** is responsible for protecting the health and providing essential human services for all Americans. Several agencies function under HHS including the Center for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ). HHS and state-level Departments of Health are responsible for developing and supervising the implementation of health policies, as well as managing a large part of health care expenditure via The Center for Medicare & Medicaid Services (CMS). However, there is no strict target of federal- or state-wide health care expenditure.
- **The Food and Drug Administration (FDA)** is a regulatory body responsible for approving and registering pharmaceutical drugs and medical products in the US, as well as monitoring their safety and efficacy while on the market.
- The **Centers for Medicare & Medicaid Services (CMS)** is the largest public health insurer, which operates Medicare, Medicaid, and CHIP. CMS sets the reimbursement rates for drugs and medical devices, as well as prospective payment rates (e.g., Diagnostic Related Group (DRG), ambulatory payment classification (APC), physician fee schedule (PFS) or by the Medicaid PFS) for the programs they operate. Reimbursement payment rates from private insurance companies are often based on CMS rates and typically are not lower than CMS reimbursement.
- The **Pharmacy and Therapeutics (P & T) Committee** develops and manages the formulary systems used in many different settings, i.e., hospitals, long-term-care facilities, Medicare, Medicaid, insurance companies, and managed care organizations. They acts as the liaison between pharmacy and medical staff in terms of choosing therapies that are effective, safe, and cost-effective for their particular facility or insurance plans.
- **Private Insurers** (Private health insurance plans) are the key operators that make purchasing, coverage, and payment decisions regarding health care services.
- **Managed Care Organizations (MCO)** or payers, operationalize health insurance for their enrollees by providing a complete health care delivery system consisting of affiliated and/or owed hospitals, physicians and other providers who provide a wide range of coordinated health services (e.g., Blue Cross and Blue Shield, United Healthcare, Kasier Permanente). These include health maintenance organization (HMO) and preferred provider organization (PPO).
- **Pharmacy Benefit Managers (PBMs)** design, implement, and manage pharmacy benefits and coverage. Payers (MCOs) often partner up with PBMs and let the latter manage pharmacy-related insurance responsibilities (e.g., Express Scripts, CVS Caremark).

USA- Decision making and pricing 1-3

- Once the manufacturer develops a product, the medicine must be reviewed for safety and efficacy to be available in the US market. Once on the market, the product is reviewed by different health care bodies that will determine the market access for individuals based on coverage and reimbursement decisions before reaching the patient.

- Before pharmaceutical products (both brand-name and generics) can be marketed in the US, they are subject to market approval by the US Food and Drug Administration. A product must demonstrate sound efficacy and safety through various phases of clinical trials, which are undertaken by the pharmaceutical sponsor and assessed by the FDA's Center for Drug Evaluation and Research (CDER) prior to regulatory approval. Trial data are evaluated by CDER to determine whether the drug is ready for sale and if the pharmaceutical company can apply for a new drug application (NDA) to introduce the medicine into the US Market.

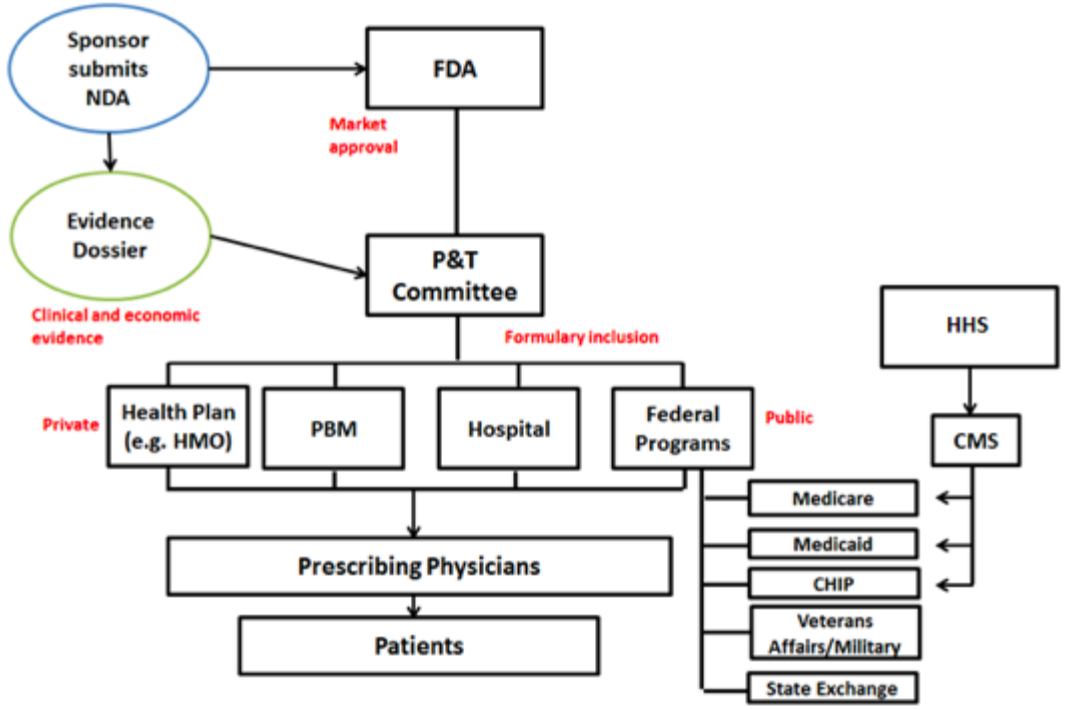
- Once approved, a medicine is available for use, but for the product to be reimbursed by a health insurance plan, it must be considered for formulary inclusion by their Pharmacy and Therapeutics (P&T) committee.

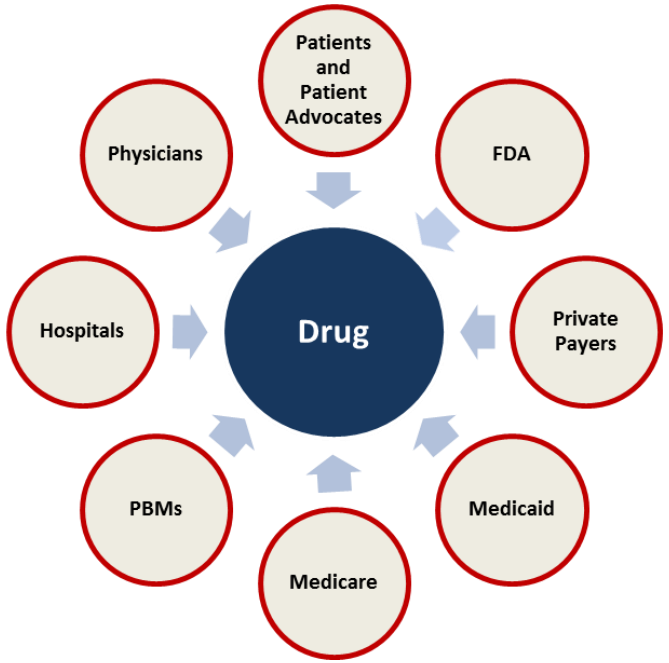
- Generally speaking, payers in the US (both CMS and private insurance companies) do not regulate the price of a pharmaceutical product, allowing the manufacturers to set prices freely. However, payers are allowed to set the reimbursement price/rate. The reimbursement process differs between the public sector (CMS) and the private sector.

USA- Decision Making 2-3

- Formulary evidence dossiers
  - Evidence dossiers summarize the key clinical and economic evidence for a product and are often used as a reference document by P&T committees for their formulary decision making, along with other key considerations such as drug acquisition costs and potential budget impact. Pharmaceutical sponsors typically develop an Academy of Managed Care (AMCP) dossier detailing key clinical and economic evidence for their product and submit it to AMCP. The dossier gets uploaded on the AMCP portal and is made available to health care decision makers (health plans, Pharmacy Benefit Managers (PBM), government agencies, etc.) upon their unsolicited request. This information is used to support reimbursement and/or formulary placement, consideration of a new product, new indication, or new formulation of an existing product
- Public sector
  - For prescription drug coverage, Medicare offers a prescription drug plan, which is offered through health plans and PBMs approved by Medicare. Similarly, Medicare Advantage Plans typically offer the same prescription coverage. These plans have their P&T committees make decisions on what drugs to include in the formulary, using the information from evidence dossiers and accounting for drug acquisition costs and potential budget impact.

USA- Decision Making 3-3





USA – case example

- Both Medicaid and Medicare have committed to support and cover cell and gene therapies for eligible patient groups.
- FDA has approved both Kymriah and Yescarta for the US market (market authorization).
- Center for Medicare & Medicaid Services (CMS) has set reimbursement at for both Kymriah and Yescarta for both outpatient and inpatient settings.
- Reimbursement rate differ per setting and range 186,500 USD to 500,000 USD.