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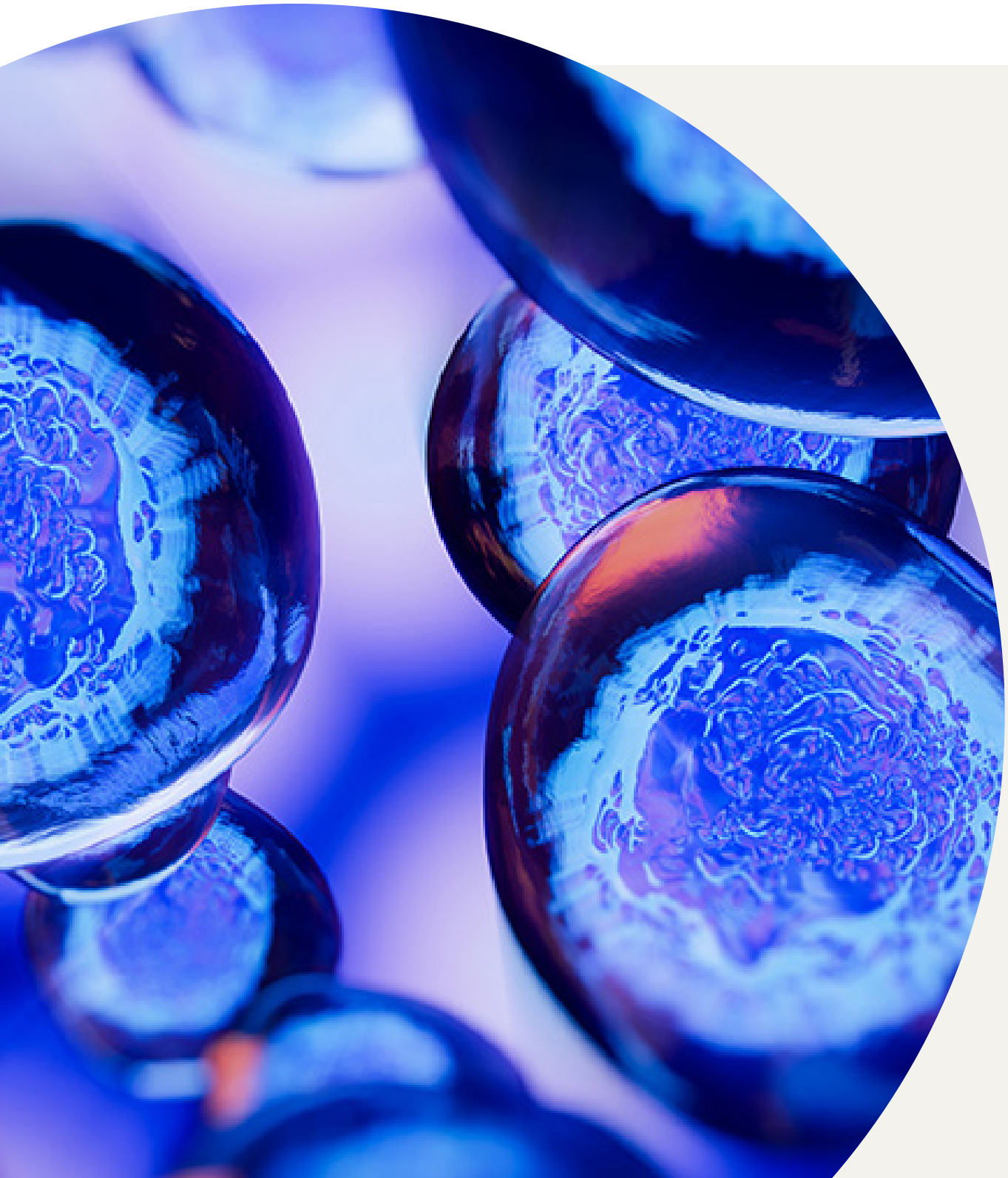
Stem Cell Therapeutics: The Need for Early Market Access

An exploration of the market access considerations manufacturers require for commercial success in regenerative medicine



Cogentia®

enquiries@cogentia.co.uk
cogentia.co.uk

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OVERVIEW OF THE MARKET ACCESS CHALLENGES ASSOCIATED WITH STEM CELL THERAPIES AND GENE THERAPIES.

According to a report published by the Milken Institute, significant growth is anticipated in the cell and gene therapy industry, with an estimated 75 therapies to be approved in the US by 2030 which suggests a rising interest towards the realm of regenerative medicine.[1]

Forecasts also indicate significant growth in the global stem cell therapy market, with projections estimating a market size of $615 million by 2028.[2] However, despite advancements, the categorisation of stem cell therapeutics remains heterogeneous, meaning it is necessary to provide clarification when defining the scope of their application.

Our whitepaper aims to provide a comprehensive overview of the stem cell therapy landscape, including a review of assets which are either currently on the market or in development, and ultimately providing insights into the market access and strategy considerations required for stem cell therapy products.

This analysis focuses only on regenerative assets, which involve the direct use of stem cell for reparative treatment. Notably, academic sources have been excluded to ensure an emphasis on industry-driven perspectives.

Main whitepaper highlights include:

- Stem cell regenerative therapies are very heterogenic, with different sources of cells and different therapy approaches (autologous/allogeneic). They can be used for virtually any therapeutic area (in phase 2 clinical trials, stem cell therapeutics currently cover over 10 different therapy areas)
- Allogeneic therapies are likely to dominate the stem cell therapeutic market given their lower manufacturing costs, currently they represent more than 70% of the phase 2 clinical trials.
- Depending on the disease and therapeutic approach (autologous or allogeneic), stem cell therapeutics can be used as a one-time treatment or administered multiple times.
- Current marketed regenerative stem cell therapies correspond mainly to skin grafts that are used for ulcers and burns.
- Only 3 marketed non-graft stem cell therapeutics have reached the market. They all target niche indications with high unmet need and perceived high willingness to pay, usually used as a last line of treatment.
- Market access planning for regenerative stem cell therapeutics is similar to other Advanced Therapeutic Medicinal Products (ATMPs), **with early planning being critical for commercial success of the asset.**
- **The main challenge for market access is the demonstration of asset value in pricing negotiations,** with uncertainties existing regarding treatment duration, similar to other one-off treatments like gene therapies.
- **It is important for manufacturers to consider the lifecycle management strategy for a stem cell therapy product as well as market access requirements and timelines.** For example, patents for stem cell therapies are focused on the technological process as opposed to the product itself, which adds complexity to the lifecycle management strategy.
- **Manufacturers who plan European commercialisation, need to be prepared for the European joint Clinical Assessment (JCA),** the biggest market trend impacting ATMPs market access process and timeline. This will be implemented in 2025, for ATMPs (which includes regenerative stem cell therapies) and innovative therapies for cancer treatment.

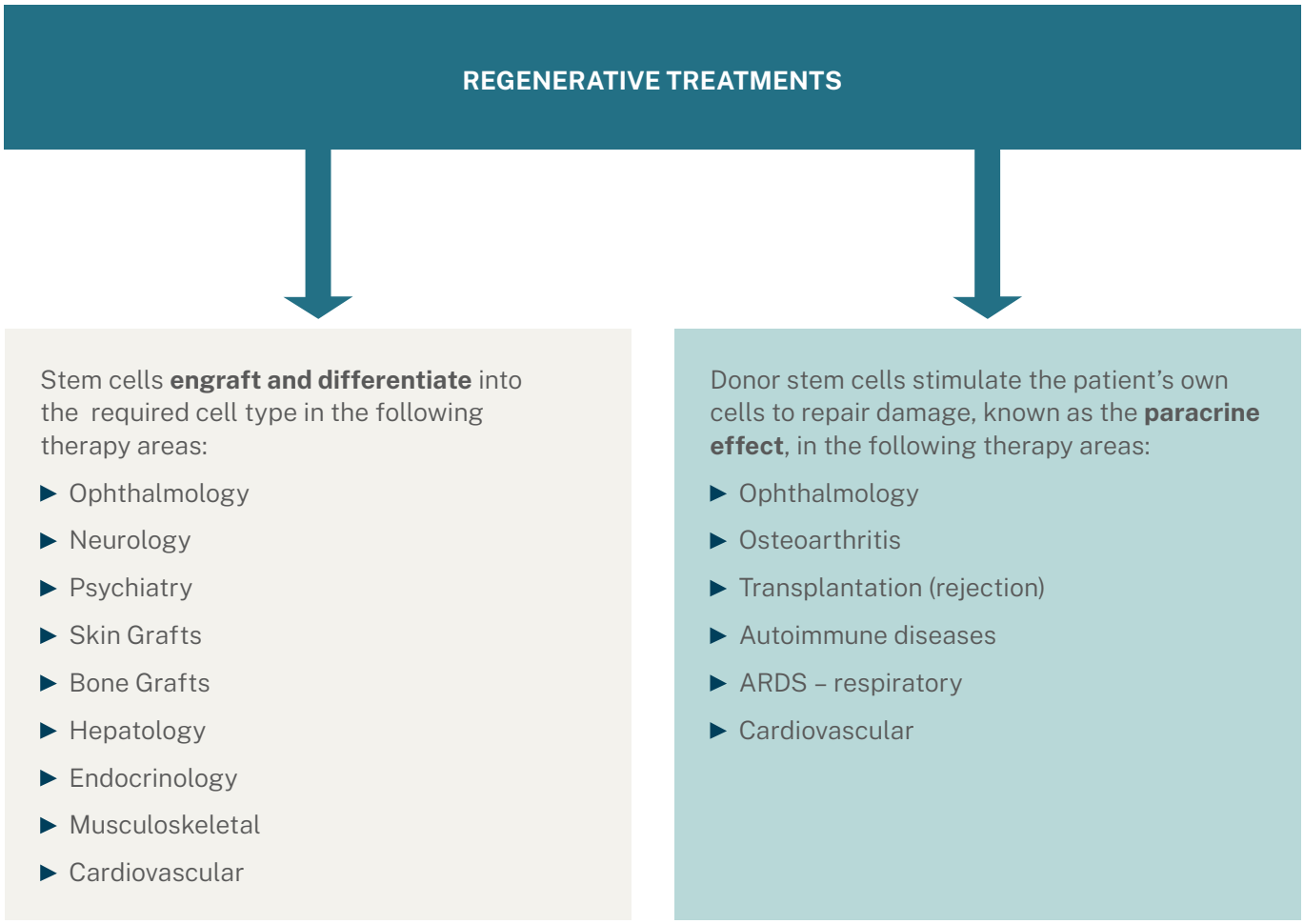
INTRODUCTION

Stem cells are undifferentiated cells that facilitate the maintenance of tissues and organs in multicellular organisms due to their ability to self-renew and differentiate into various specialised cell types. As of December 2023, the global stem cell therapy market was valued at $286 million, with projections indicating a potential increase to $615 million by 2028.[2]

Therapeutic products incorporating stem cells fall under the regulatory remit of regenerative medicine, a rapidly evolving field involving the repair, replacement, or regeneration of damaged cells, tissues, or organs in the body, with the goal of restoring their original function.

For the purpose of this whitepaper, Cogentia's analysis focuses on regenerative stem cell therapies which involve the direct use of stem cells for reparative treatment (Figure 1).

Figure 1. Regenerative treatments included in whitepaper analysis



Source: Adapted from information on the Parent's Guide to Cord Blood and Mayo Clinic's websites.[3,4]

The main sources of stem cells for regenerative medicine include embryonic, foetal, adult and induced pluripotent stem cells (derived from differentiated somatic cells that have been genetically modified) (Table 1). Interestingly, adult stem cells formed 83% of the stem cell market in 2022,[5] likely due to their favourable properties, which include the absence of graft rejection in autologous cells as well as lack of ethical concerns.

In addition, stem cells may be further categorised as either 'autologous' or 'allogeneic' depending on their origin. Therapies adopting an autologous approach utilise the patient's own stem cells for treatment; whereas allogeneic approaches rely on donor stem cells, which are either matched-related or unrelated to the patient. Each approach offers various benefits and limitations in terms of the risk of graft versus host disease (GvHD), infections, tumorigenicity, cell yield and ethical considerations, as shown in Table 1.

Table 1. Characteristics of stem cells used in regenerative medicine

	PARAMETERS	TYPES OF STEM CELLS				
TYPE OF CELLS		EMBRYONIC	TISSUE DERIVED			
ORIGIN OF CELLS		Embryos	Induced Pluripotent	Foetal	Adult	
PROPERTIES OF STEM CELLS	AUT/ALL	ALL	ALL	ALL*	ALL	AUT
	Risk of GvHD					
	Risk of infections					
	Tumorigenicity					
	Cell Yield	Unlimited	Unlimited	Low	Moderate	
	Ethical Concern	Yes	No	No	No	

Low Risk/ High Benefit | **Moderate Risk/ Benefit** | **High Risk/ Low Benefit**

Abbreviations: PSC: pluripotent stem cell.

Notes: *Perinatal (infant) stem cells are primarily allogeneic, however may also be autologous in certain cases (rare). Stem cell categorisation is complex and subjective; therefore, a non-exhaustive selection of stem cell types and origins has been provided for simplicity.

Risk of GvHD: A potentially serious complication of allogeneic stem cell transplantation which occurs when donor stem cells known as 'the graft' attack healthy cells in the transplanted patient ('the host'). The risk of GvHD is greater if patients receive allogenic stem cells (from a donor). However, stem cell source can also influence the risk of GvHD, for example, using foetal stem cells (i.e., from umbilical cord blood) lowers the incidence of GvHD.

Risk of Infections: The risk of opportunistic infections is lower following an autologous stem cell transplantation compared with an allogeneic stem cell transplant, since donor stem cells are not present.

Tumorigenicity: Certain stem cell types (i.e., embryonic and induced pluripotent) are more likely to produce tumours (tumorigenic) upon cell division, due to their ability to differentiate into any specialised cell type. Foetal and adult stem cells are less likely to be tumorigenic as only certain specialised cell types can arise following proliferation.

Cell Yield: Adult and foetal stem cells have a more limited ability to differentiate into any specialised cell type, compared to embryonic and induced pluripotent stem cells which can differentiate into any type of cell (higher cell yields).

Ethical Concern: Embryonic stem cell research and use can be argued as unethical since cell derivation involves the destruction of a human embryo.

Sources: Based on information from Barzegar et al. (2019)[6], Torre and Flores (2021)[7] and information from Merck's Website.[8]

STEM CELL THERAPY PIPELINE AND DISEASE AREAS TARGETED

Cogentia have conducted an analysis of all stem cell therapy assets, including those currently available on the market or in developmental Phases 1, 2 or 3, using the Evaluate Pharma platform.

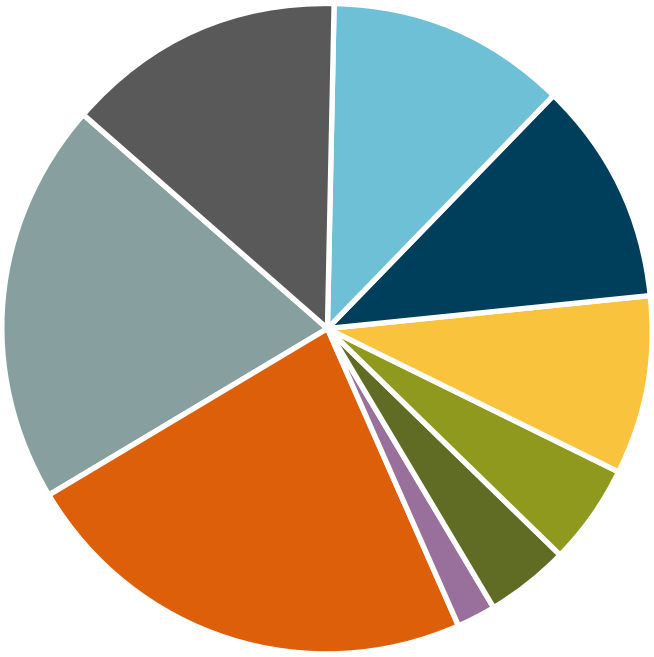
Our analysis focuses on regenerative assets, as outlined in Figure 1, which involve the direct use of stem cells for reparative treatment. It is important to note that our pipeline analysis is non-exhaustive since it does not include multiple sources beyond Evaluate to capture current ongoing academic research.

Following a thorough review of the stem cell therapeutics currently in development, a diverse pipeline emerges, featuring over 200 assets which span more than 10 therapeutic areas. These assets are targeting various stem cell types, ranging from neuron and muscle cells, through to others such as bone. We directed our focus towards products in Phase 2 trials, since they offer the near-term representation of how the stem cell market will develop.

As highlighted in Figure 2, over 10 therapeutic areas are targeted by regenerative stem cell therapies in Phase 2 trials, with significant focus on treatments in neurology, immunology, cardiovascular diseases, and orthopaedics. A previous analysis of the gene therapy clinical trials landscape (Cogentia Whitepaper 2021[9]) reveals differences in target therapeutic areas between these two technology types (Figure 2). Both stem cell and gene therapies appear to have a significant proportion of clinical trials focusing on neurology. Stem cell therapy trials are also largely made up of immunology, cardiovascular, orthopaedic and respirology therapy focuses. This contrasts to gene therapy which has a large proportion of trials in metabolic, ophthalmology and musculoskeletal therapy areas (Figure 2).

Figure 2: Therapeutic areas being targeted in stem cell and gene therapy clinical trials

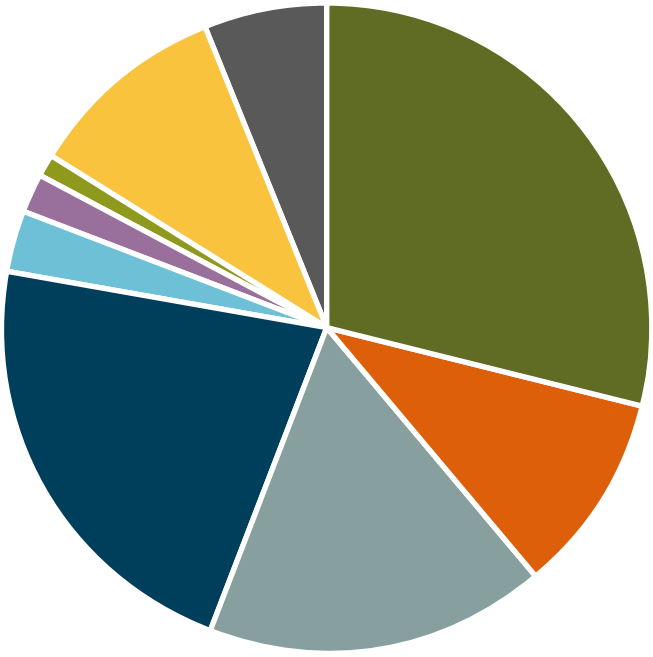
Stem Cell Therapies:



- Cardiovascular 14%
- Orthopedics 12%
- Respirology 11%
- Hepatology 9%
- Metabolism & Endocrinology 9%
- Dermatology 4%
- Rheumatology 2%
- Neurology 23%
- Immunology 20%

Source: Pipeline analysis obtained from Evaluate Pharma (2023).[10]

Gene Therapies:

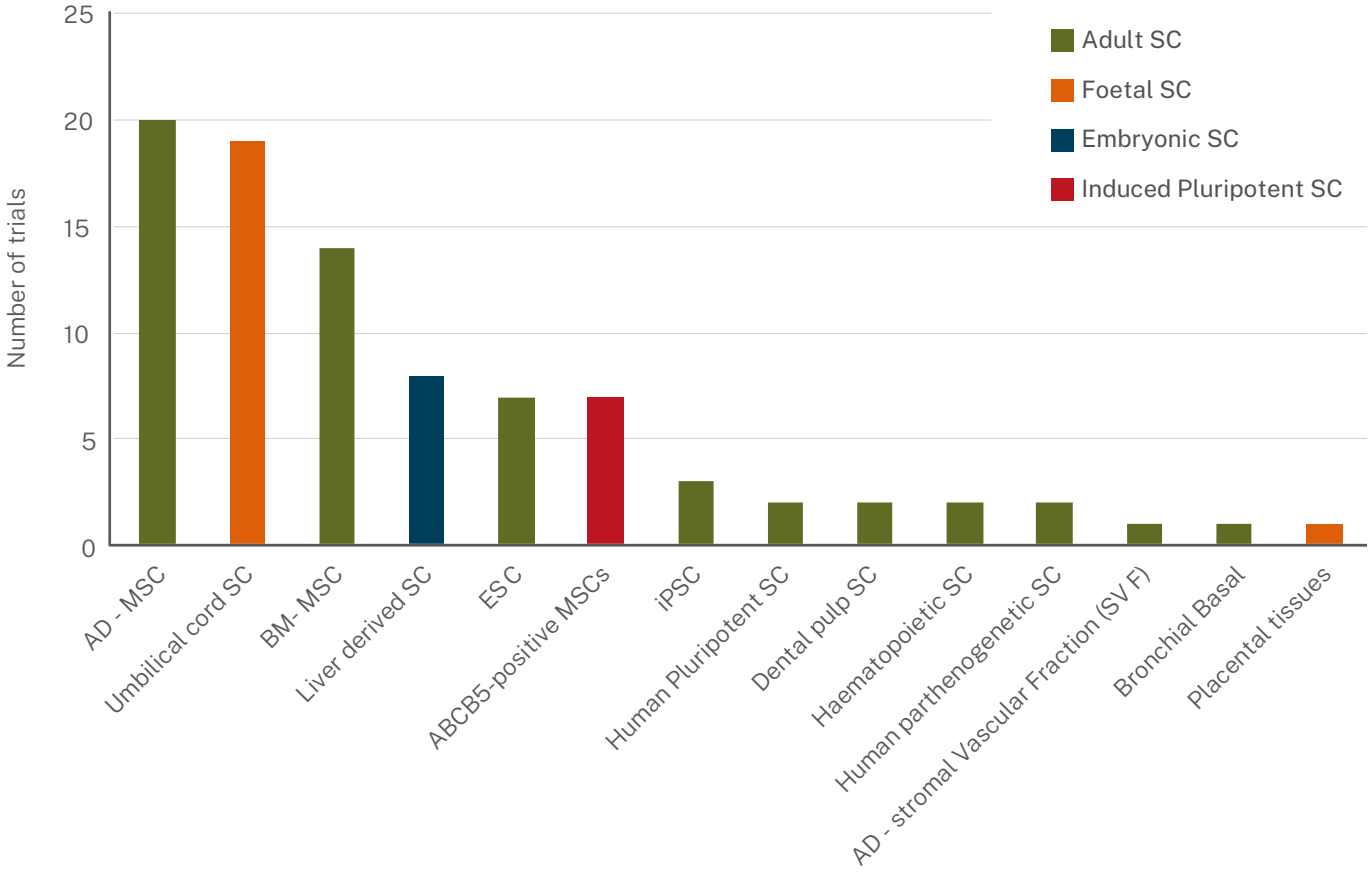


- Metabolic 29%
- Musculoskeletal 10%
- Neurology 17%
- Ophthamology 22%
- Cardiovascular 3%
- Dermatology 2%
- Endocrinology 1%
- Haematology 10%
- Immunology 20%

Source: Cogentia Gene Therapy Whitepaper (2021).[9]

All the stem cell origins in Table 1 are represented in the clinical trial landscape. Adult and foetal stem cells are the most common sources used in the development of new therapeutics, which is likely driven by their low risk of tumorigenicity compared to the other stem cell sources (Figure 3).

Figure 3: Phase II stem cell clinical trials by source of tissue



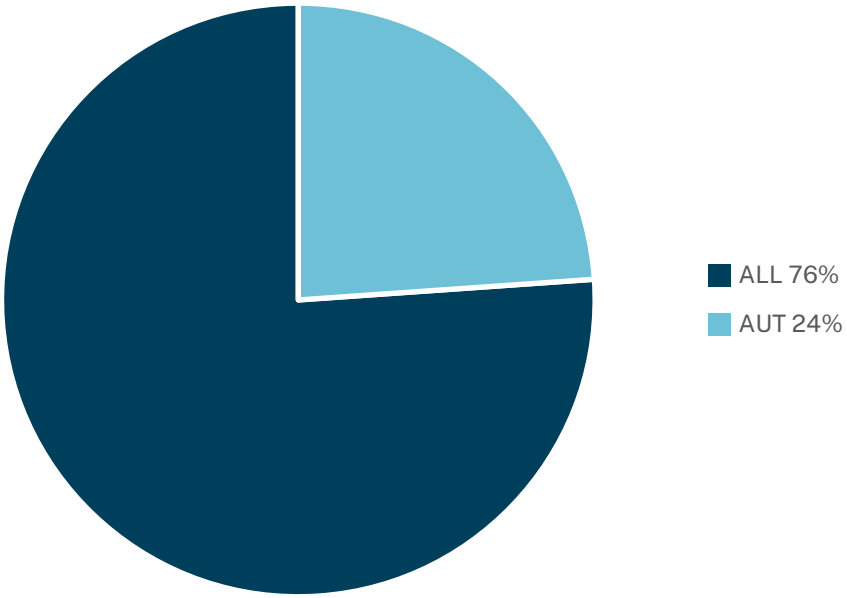
Abbreviations: AD: Adipose derived; BM: bone marrow; ESC: embryonic stem cell; iPSC: induced pluripotent stem cells; MSC: mesenchymal stem cells; SC: stem cells; SVF: stromal vascular fraction.

Notes: Stem cell categorisation is complex and subjective; therefore, we have only considered four overarching categories for simplicity. Reference to ABCB5 relates to a specific gene.

Source: Pipeline analysis obtained from Evaluate Pharma (2023).[10]

Interestingly, the majority of stem cell therapy assets are allogeneic as opposed to autologous, and allogeneic assets represent more than 70% of the total number of products identified in Phase 2 clinical trials (Figure 3).

Figure 4: Phase II stem cell assets – allogeneic versus autologous



Source: Pipeline analysis obtained from Evaluate Pharma (2023).[10]

Autologous treatments require multiple steps involving gaining access to the patient's cells, purifying/manipulating them in the lab and placing them back into the patient. The level of complexity and costs limits autologous therapeutics to niche and high-priced indications, usually composed of one-off therapies. Instead, in allogeneic treatments patients get cells from a donor, and it is possible to amplify the donor cells to be used in multiple patients. This way, allogeneic therapies have lower manufacturing costs, which provides more opportunity for these treatments to access higher volume indications with the potential to use price-volume access negotiations. Allogeneic stem cell therapies could also be used in chronic treatment as long as they do not cause immunogenicity. This is relevant specially for therapies which act via the paracrine effect, effectively stimulating patient's own cells to repair themselves. These differences could therefore explain the considerably higher proportion of allogeneic therapies in the stem cell Phase 2 clinical trial pipeline (76%).

Looking at the geographical distribution of manufacturers' headquarters leading Phase 2 clinical trials, the United States, South Korea, and China appear to be frontrunners in regenerative stem cell therapeutics. Collectively, these countries (specifically the manufacturing company headquarters) are responsible for 73% of the Phase 2 clinical trials for regenerative stem cell therapy assets (Table 2). This is not necessarily representative of the initial development location, as this data can be impacted by the acquisition of international biotechs by US headquartered companies.

Table 2: Top 5 countries with manufacturing company headquarters responsible for regenerative stem cell Phase 2 clinical trials

COUNTRIES (COMPANY HEADQUARTERS)	# OF TRIALS	% OF TRIALS
US	21	24%
South Korea	14	16%
China	11	12%
Belgium	11	12%
Japan	8	9%

Source: Pipeline analysis obtained from Evaluate Pharma (2023).[10]

Although the majority of stem cell therapies are still in clinical development, there are 13 marketed regenerative stem cell products, and over 50% of them are grafts (either skin or bone grafts). Over half (62%) of the marketed stem cell therapeutics (8 out of 13) are owned by companies headquartered in Asia, with South Korea being the country with most marketed stem cell therapeutics. In contrast to the Phase 2 assets, the marketed regenerative stem cell therapeutics are 50/50 split between autologous and allogeneic therapeutics.

A deep dive on 3 of the 13 marketed stem cell (Neuronata-R, Holoclar and Alofisel), which corresponds to products that have received regulatory approval and are not skin or bone grafts, is presented in Table 3.

Table 3: Details of marketed stem cell products (non-graft only)

PRODUCT	MANUFACTURER	AUT/ALL	APPROVAL ENTITY	INDICATION	LINE OF TREATMENT	REIMBURSED?	PREVALENCE	PRICE	SALES
Neuronata-R (lenzumestrocel)	Corestem	Autologous	KFDS (South Korea)	Delay ALS progression	Not defined	No	~19.7/100,000[11] (Rare disease)	~U$55,000[12,13]	>U$16.5 M since launch in 2015[12,13]
Holoclar	Holostem	Autologous	EMA (EU)	Severe eye damage (limbal stem cell deficiency)	Last line	Partial (No Reimb. in Spain)[16]	~3/100,000 (Ultra – rare)[14]	~$92,000[15]	N/A (privately held company)
Alofisel (darvadstrocel)	Takeda	Allogeneic	EMA (EU)	Complex anal fistula in Chron's disease patients	Last Line	Partial (Reimb. in Spain)[16]	~7.6/100,000 (Rare disease)[18]	U$55,000 – 65,000[15]	U$3.5M Jun '21 sales[17]

Notes: Neuronata-R sales were calculated based on over 300 patients since launch (private market).[12]

Source: Pipeline analysis obtained from Evaluate Pharma (2023)[10]; Wolfson, C. et al. (2023)[11]; Korea Biomed news website[12,13]; NICE Holoclar assessment[14]; Pharma[14] pricing platform[15]; Ronco, V. et al (2021)[16]; Gene online website[17]; Garcia-Olmo, D. et al (2019).[18]

These products have been approved by two regulatory agencies, EMA and KFDS, and have been developed by manufacturers based in their local markets, except for Takeda which is a global company headquartered in Japan. All products have been focused on low prevalent indications (rare diseases) and have not achieved broad reimbursement in their local markets. Each product has a different therapeutic area, in either neurology, ophthalmology or gastro-intestinal (immunology). Various treatment approaches are also used, with two products using autologous stem cells and the third adopting an allogeneic approach (Table 3).

The marketed product prices range between $55,000 and $90,000 per annum. Only Holoclar and Alofisel which target last-line treatment have achieved some sort of reimbursement in Europe.

MARKET ACCESS CONSIDERATIONS FOR MANUFACTURERS

For stem cell therapies to reach the projected market value of $615 million by 2028, developmental assets must not only secure regulatory approval but also achieve successful pricing and reimbursement. At present, there are very few marketed stem cell therapy products, and despite some similarities existing with other advanced therapies such as gene therapies, unique market access challenges are apparent.

Table 4 highlights a non-exhaustive list of the unique market access challenges associated with stem cell therapies, in our opinion capturing the most important hurdles manufacturers may face throughout their journey towards product launch.

Table 4 presents these challenges from the industrial perspective, but it is important to consider that market access involves numerous other stakeholders, for example, payers, hospitals, clinicians and patients and their carers. Their respective needs and preferences should be considered in developing the access strategy and planning commercial launch.

Table 4: Overview of the market access challenges associated with stem cell therapies and gene therapies

STEM CELL THERAPIES		
ACCESS CHALLENGE	**SIMILARITIES VS GENE THERAPIES**	**DIFFERENCES VS GENE THERAPIES**
(1) Indication Targeting	There is a need to select an indication with an unmet need	There are many potential target indications that could be selected (SCT can target any cell in the body)
	There is a need to select an indication that has commercial value	The choice of development indication from a long list is crucial to funding (since many SCTs are developed by early-stage biotech)
(2) Asset value considerations	The approach to assessing value is the same for all products	There is a greater ease of scalability (compared to gene therapy) which could result in differing price expectations between manufacturers and other stakeholders
	Both types of products are often considered to be one-time, long-lasting treatments (autologous stem cells)	Allogeneic SC products – potentially to be administered more frequently (than one-time) unlike GTs (industry & payers)
(3) Asset pricing	The price of a product in a given market is based on value following assessment process	There is a greater ease of scalability (compared to gene therapy) which could result in differing price expectations between manufacturers and other stakeholders (allogeneic stem cells)
	Both public and private healthcare settings can be considered for launch	There are no solid benchmarks for pricing stem cell therapies
(4) Lifecycle management of the asset	Lifecycle management strategy and sequencing need to be considered prior to commercialisation	Patents apply to processes rather than to products
		Indication sequencing must account for a greater choice of potential therapy areas (potentially in different therapy areas)
(5) Evidence requirements	Evidence requirements similar to cell & gene therapies	
	Uncertainties in duration of effect	

Abbreviations: GT: gene therapy; SC: stem cell; SCT: stem cell therapy.

CHALLENGE (1) – HOW TO SELECT THE APPROPRIATE INDICATION?

Neuronate-R is an interesting case study. Neuronata-R is a stem cell therapy product developed in South Korea which delays the advancement of amyotrophic lateral sclerosis (ALS). It was first commercialised in South Korea by Corestem following a conditional authorisation by the Korean Food and Drug Regulatory Agency back 2014. Fast forward to 2018, after failing to achieve reimbursement in the South Korean public market, Corestem decided to pivot their strategy to focus on international markets "which are highly active in their policy considerations of innovative treatment for patients with rare diseases," having received orphan drug designation status from FDA (2018) and EMA (2019). Corestem is currently running Phase 3 clinical trials to support the submission in international markets.

With careful consideration of the global market landscape and pharmaceutical opportunities, Corestem may have been able to accelerate their product commercialisation and maximise the market opportunity of their asset.

Cogentia has previously developed a "commercial attractiveness" matrix, which we presented in our Gene Therapy whitepaper back in June 2021 (Table 5). The application of this matrix approach is very applicable for stem cell therapies, and we would recommend its use very early in the asset development process.

Table 5: An example "commercial attractiveness matrix" developed for gene therapy assessment

DISEASE AREA	PREVALENCE	AGE IN CLINICAL TRIALS (YEARS)	DISEASE BURDEN	DIRECT TREATMENT COSTS	CURRENT TREATMENT OPTIONS	COST OF COMPARATOR/ YEAR*	HIGH PRICE PRECEDENT Y/N
Parkinson's Disease	~10 million worldwide	30-75	Symptoms include uncontrollable tremors, bradykinesia, deteriorating cognitive function	$30-60k per year. Includes hospital inpatient + outpatient appts, non-acute institutional care	Carbidopa-levidopa, deep brain stimulation	$50-100k (one off)	N
Wet AMD	~3 million worldwide	50+	Most people move from diagnosis to legal blindness in 10 years without treatment	$10-20k per year, including diagnostic and assistance with daily activities	Lucentis, Eylea	$20-40k	N
Duchenne Muscular Dystrophy	5/100,000	4-7	Rapidly progressive, lethal neuromuscular disorder. Common to be wheelchair-bound by age 8-14. Life expectancy <30 years	Ranging from $10k-80k per year as disease progresses	Corticosteroids, Viltepso, Exondys 51, Vyondys 53	$300k-$1m	Y
Haemophilia A	5/100,000	18+	Life expectancy around normal with extensive treatments	BioMarin put the cost of lifetime treatment of haemophilia A at $25m	Factor VIII, Hemlibra	$400-$700k	Y
MPS Type I	1/100,000	4 months+	Significant developmental delay + cognitive decline. Life expectancy <10 years	Poorly documented, likely to be well over $100k per year in severe disease	Aldurazyme/HSCT	$200-500k	Y
Fabry Disease	10/100,000	16-50	Type 1 leads to excruciating pain in extremities, and progressive renal insufficiency. Life expectancy 58-75 years	~$60k per year, including hospital admissions, surgery, diagnostic imaging, ERT	Fabrazyme, Galafold	$200-400k	Y
Cerebral Adreno-leukodystrophy	2/100,000	>17 years	Progressive neurological symptoms with rapid loss of function. Life expectancy in childhood CALD 5-10 years post-diagnosis	Poorly documented. Estimated at >$100k/year driven by 24/7 care	HSCT	$150-200k (one off)	N
Sickle Cell Disease	30/100,000	12-35	Sickle cell crises, infections, anaemia with vaso-occlusive crises. Life expectancy 45-50 years	~$60k per year, higher depending on number of VOC	Adakveo, Oxbryta	$100-150k	Somewhat
SMA Type I	10/100,000	<6 months	Type 1 is typically fatal within 2 years, and involves a lack of developmental milestones	$100-200k per year, driven by hospital visits, rehabilitation and other costs	Spinraza, Evrysdi	$350-750k	Y
GM1 Gangliosidosis	0.5/100,000	0.5-12	Type 1 is the most severe, characterised by developmental regression. Life expectancy in type 1 is 2-3 years	Varies based on type. Type 1 has costs ~ $150-200k/year	No approved treatment	–	N

Assessment based on Cogentia review of published sources. Disease prevalence taken from Orphanet, with the exception of Parkinson's disease and wet AMD. Other costs and descriptive text based on analysis of public sources. Colour coding spans commercially favourable (deep green) to commercially unfavourable (orange). All comparisons are relative and based on subjective assessment. Other reviewers may come to different conclusions. Disease burden based on more severe forms of disease, where gene therapies would be used. Costs of comparators based on US prices. Scores are assigned to each disease area using colour coding with dark green worth 4 points, mid-green worth 3 points, light green 2 points, yellow 1 point and orange 0 points.

Note: A similar format is recommended for assessing stem cell therapeutics.

Source: Cogentia Gene Therapy Whitepaper (2021).[9]

Of the characteristics shown in this matrix, the main elements which are particularly relevant for manufacturers to consider when deciding on an indication for their stem cell therapy assets include:

1 **Prevalence:** the disease should be relatively prevalent in rare disease terms, but not so prevalent that payers baulk at a price anywhere above five figures. Autologous treatments are probably restricted to rare diseases. Allogeneic treatments, taking advantage of the economies of scale, could permeate into more prevalent diseases if they can overcome budget impact considerations from payers.

2 **Disease Burden:** the disease should be severely debilitating, or the cell therapy should be targeted at the most severe form of the disease (for example, reimbursement of Holoclar and Alofisel in Europe is restricted to last line of treatments).

3 **Healthcare Resource Use:** resource use should be high with significant cost-savings expected in those who receive an innovative treatment to maximise potential pricing of the treatment.

4 **Current Treatment Options:** options should be limited and not considered to be effective, potentially with challenging safety profiles and questions over benefit: risk ratio.

5 **Cost of comparator:** comparators should be expensive, setting a precedent for high pricing and offering a simple like-for-like cost offset for budget impact estimates.

Having examined three marketed stem cell therapeutics, we can add the following challenges relating to the heterogeneous nature of these therapies:

a) They can potentially be developed to target virtually any cell type.

b) They can be one-off (like gene therapies) or chronic treatments (like traditional biologic and small molecules treatments).

c) Potential for wide variability in manufacturing costs between autologous and allogeneic technologies.

The highly heterogeneous and diverse stem cell therapy pipeline requires both clinical and market access expertise, ensuring that developers have considered all of the elements outlined above, as well as the interactions between these factors.

In our experience having a round table, multidisciplinary approach to the early decisions and targeting is critical to avoid issues with market access further down the line during later product development stages and market launch.

Activities for Manufacturers to Consider Include:

- Indication landscaping
- Commercial attractiveness matrix

CHALLENGE (2) – HOW TO VALUE A STEM CELL THERAPY ASSET?

In addition to the purely commercial considerations highlighted in Cogentia's "commercial attractiveness matrix", it is also necessary to understand the impact of market specific value assessment and negotiation frameworks.

Across the biggest healthcare markets (US and EU), regenerative stem cell therapeutics will be faced with an established value-based negotiating framework that has been put in place for traditional therapeutics.

For one-off autologous stem cell therapeutics, we expect manufacturers to face similar challenges that have been seen with commercialised gene therapies. The greatest challenges to date have been in supporting the long-term duration of efficacy and the accrual of the benefit into a single payment at the outset of treatment.

Manufacturers can take advantage of the available Manage Entry Agreements (MEA) models that have been put in place to overcome the pricing and reimbursement challenges faced by other ATMPs, such as outcome-based agreements, price-volume agreement, and capitation agreements. In Table 6 we present a list of MEAs from our previous whitepaper.

Table 6: Examples of Managed Entry Agreements used for pharmaceutical products

MEA	EXAMPLE	COMMENTARY
Pay-for-performance risk share	CAR-T therapies in Germany	Ensure payment is contingent on a realised clinical benefit
Annuity-based payments	Zolgensma in the US	Spread the cost over multiple years, but no ability to leverage evidence generated post-approval
Outcomes-based agreement	Zynteglo in Germany	Allows manufacturers to retain a high price assuming clinical benefit exists. Helps to generate RWE for both parties
Dose cap	Revlimid in the UK	Simple measure to limit budget impact
Free initial doses	Spinraza in Italy	Useful for drugs that require a loading dose that results in a higher first year cost
Portfolio element	Vertex in the UK	Allows rapid access to multiple therapies, uncommon approach
Confidential discount	Common in most countries	Manufacturers can maintain a high list price, simple and easily transactable MEA often preferred by payers
Price-volume agreement	Particularly common in France	Helps to control budget impact by ensuring trade-off between price and volume
'Netflix' subscription model	Antibiotics in the UK	Payment can be based on the value provided by a treatment rather than how much is used

Notes: Examples are illustrative of managed entry agreement options available to manufacturers and include examples from gene therapies as well as other treatment modalities.

Source: Cogentia Gene Therapy Whitepaper (2021).[9]

Moreover, in a world where individuals can gain an edge through the use of performance enhancing drugs, the potential of stem cell therapy may be extended beyond that of curative benefit in clinical settings. But will payers and healthcare systems be prepared to pay for additional benefits beyond cure or a set norm? Would these additional elements of value be treated differently; would they be similar to many "lifestyle" type treatments or would there be a willingness to change current value frameworks?

It will be necessary for manufacturers to define the value and price of their therapeutic based on the existing value-based frameworks, whilst tracking and adapting it to any market specific developments. If manufacturers perceive a greater benefit than can be realised outside of these frameworks, there may be a need to consider commercialisation in the private healthcare market, where the volume might be smaller, but willingness to pay could be higher.

Activities for Manufacturers to Consider Include:

- Opportunity Assessment
- Forecast Modelling

Only time will tell whether the new wave of regenerative stem cell therapeutics will lead to the development of a new value-based framework appropriate for a host of relevant diseases, and potential improvements beyond just restoration.

CHALLENGE (3) - HOW TO MAXIMISE THE PRICE OF A STEM CELL THERAPY ASSET?

The pricing of innovative pharmaceutics can be a very complex topic, but in essence there are two elements in tension: the market or payer willingness to pay and the overall return necessary to incentivize developers to undertake the research and development. Therefore, there has to be a "sufficient" margin over manufacturing costs.

There needs to be an area of common ground where the payer is getting value (price within their willingness to pay for those patient and societal benefits), and where the manufacturer is getting a return based on the margin and volume sold. Given the significant costs involved in R&D, and the risks, and often the relatively low patient numbers, it will be important that the margin between net price and manufacturing costs is sufficient.

There is no one size fits all, but considering this early in the development process is critical to ensure success, even though there is significant uncertainty on price, outcomes and manufacturing and supply costs.

As mentioned in the previous section, existing value-based frameworks have been in place for many years and differ between markets and payer archetypes. The most common value-based frameworks assess the clinical efficacy and added benefit of a product. We expect payers to use the current frameworks to evaluate value and negotiate pricing for regenerative stem cell therapeutics, as they are doing for other ATMPs.

Given this we recommend an early assessment on potential price range – which would be based around these frameworks, comparators, unmet need, and also what the potential Target Product Profiles (TPPs) could be.

This can then be considered in conjunction with likely manufacturing and development costs, and risk factors, as well as cost of capital, and potential patient numbers in order to evaluate a clear economic case for development. This also can highlight the targets and thresholds for what long terms costs would need to be.

The simple outcome of this is the development of these expensive autologous stem cell therapeutics is generally directed towards indications with the highest price potential, usually those targeting higher unmet need areas (by severity or last line of treatment) and/or indications with high current treatment costs which can support cost offsets, as described in Cogentia's "commercial attractiveness matrix".

As is the case for autologous cell or gene therapies, autologous stem cell therapeutics have limited potential of reduced costs based on economies of scale. The net effect is a narrowed focus on niche/rare disease indications where the willingness to pay is very high.

In contrast Allogeneic stem cell therapeutics offer some economies of scale that could reduce manufacturing costs at volume and provide manufacturers greater room to target less severe indications, usually associated with larger patient populations. With this opportunity comes an increased need for manufacturers to be strategic when defining the sequential list of indications and evaluate the benefit-risk analysis of different scenarios.

Ultimately the key is to understand the optimal price, where returns can be maximised and to apply that back into the development and manufacturing process.

Activities for Manufacturers to Consider Include:

- Payer Research
- Asset price ranging
- Competitive landscape & comparator analysis

There would therefore seem to be a greater commercial opportunity for allogeneic stem cell (wider margins, wider potential feasible targets) as shown by the dominance of ALL therapies in the Phase II clinical stage as reviewed above.

CHALLENGE (4) – WHAT TO CONSIDER IN THE ROLL OUT AND LIFECYCLE MANAGEMENT STRATEGY?

Lifecycle management of a pharmacological asset supports the pursuit of maximising revenue potential throughout its product lifecycle.

Building on the opportunities of developing some economies of scale, from the last section, the value of an asset can be maximised through incremental indications or widening the reach and use of the product. Therefore, this element of value should be considered when evaluating what to develop and in what, when and where.

The biggest turning points in an asset lifespan are the patent and off-patent period. The patent period refers to the limited protection period of the intellectual property for the asset, generally comprised of 20 years from the filing date of the patent. During this time the inventors have exclusivity rights for the product/process invented and protected by the patent. After patent expiry, the intellectual property is not enforceable, and anyone can use/produce the process/product.

A patent contains “claims” that define the scope of protection. There are different types of claims, which can be broadly divided into two main categories: product claims and process claims. Product claims protect “things”, whereas process claims protect “ways of doing things”.

A product claim is the strongest, since it offers protection against any unauthorised party making (irrespective of the method used), using, selling, offering to sell, importing, or keeping the patented product. Process claims are sometimes considered to be inferior to product claims, as process claims notoriously suffer from enforcement issues.

The human body, at the various stages of its formation and development, does not constitute a patentable invention. Stem cell therapy products are therefore protected by process patents.

During the patent’s life we expect regenerative stem cell therapeutics to have the same type of lifecycle management approaches as other advanced therapeutics.

One key lifecycle management decision is around indication sequencing, where companies need to make a decision of which indications, when to begin and in what order. This requires careful evaluation (similar to the commercial analysis matrix), balancing the profits and cost analysis, the aspect of time and value inflection points, clinical, and technical risk, investment and financial risks and considering multiple uncertainties.

Generally, the approach is to launch with a high price and in a niche indication, later expanding into larger indications which may require lowering the price over time.

As mentioned before, allogeneic stem cell therapeutics are especially suited for expanding into broader indications that may have a lower expected price point, given the potential to achieve economy of scale and reduce manufacturing unit cost.

Besides considering indication sequencing, manufacturers will also need to consider country launch sequence. Given the highly innovative nature of stem cell technologies, it is expected that manufacturers will prioritise the launch in countries where they can achieve a higher reimbursed price.

Activities for Manufacturers to Consider Include:

- Indication landscaping
- Payer Research

Advanced therapeutics can be difficult to copy once the originator has lost the exclusivity right, especially in cases where the process involves stem cells undergoing highly specialised steps. Loss of sales after loss of exclusivity in these cases is therefore expected to be slower compared with the loss of sales seen with other biologics after the loss of exclusivity.

CHALLENGE (5) – WHAT IS THE QUALITY OF EVIDENCE REQUIRED FOR A STEM CELL THERAPEUTIC?

For the commercialisation of new medicinal product there are two main milestones that need to be achieved: regulatory approval and reimbursement. Each milestone has unique evidence requirements.

As with any new treatment, regulatory approval gives particular attention to clinical efficacy and safety data. Given that regenerative stem cell therapies are a new therapeutic class, they are likely to face additional challenges around safety in comparison to other more traditional classes.

Payers require robust evidence to determine the value of the product in relation to standard of care (SoC) or alternative treatments for a particular indication. This ultimately serves as the basis for the pricing negotiations.

Consideration of the level/ quality of evidence required depends on numerous factors and it is particular to each payer archetype. It is therefore important that a detailed landscape of requirements is recommended, which includes payer evidence requirements. Some of the factors that should be considered are:

Choice of comparator: The evidence must be applicable to the target indication, considering unmet need/ severity of the disease and potential comparators already on the market, or the lack thereof. Additional evidence challenges can present when targeting an indication without alternative treatment options. For example, it may only be practically and ethically possible to collect evidence from a single arm trial, as has been seen for some gene therapies targeting severe paediatric indications (i.e., Zolgensma). Alternatively, standard of care may comprise of a flexible basket of therapies, adding additional complexity to the clinical trial design.

Choice of endpoints: Clinical trials need to be designed specifically for an indication to highlight the value of the product for the payers. This does not necessarily correlate with the trial design required for regulatory approval. Common criticisms of trials hinge on the measurement of clinically relevant endpoints. In addition to tensions between regulatory and reimbursement requirements, there is also more weight given to the type of endpoint in some markets. For example, in large European markets such as Germany and France, payers expect to see morbi-mortality endpoints rather than so-called “surrogate” endpoints.

Duration of trial: Given the potential for long-term duration of effect for single administration therapies such as gene therapies or autologous stem cell therapies, manufacturers will need to define how long their trial collects evidence for. It is possible that payers will restrict the value of a product if it cannot effectively demonstrate its long-term efficacy.

Payer archetypes: Each payer has different appreciation on the level evidence required to overcome the data uncertainty, therefore the manufacturer needs to be able to understand this and develop the launch strategy accordingly. For example, it is known that in Germany and France HTA processes are based on an added value-based pricing that requires a comparative clinical trial on a clearly defined patient population to be conclusive. Similarly, the acceptability of managed entry agreements or confidentiality of other commercial agreements may change the company strategy. This is true for all products but is exacerbated in the example of stem cell therapy given their potential for immense clinical benefit over a long period of time.

Asset pricing/budget impact: Healthcare resources are often limited, and the role of payers is to assess priorities and maximise the healthcare outcomes based on the available resources. The quality of the evidence enables payers to make an informed decision about price, and which treatment to place the patient on (i.e., greater willingness to pay). Stem cell therapy treatments are often expensive therefore it is crucial to clearly communicate product value via efficacy, safety and long-term data to ensure payers do not lean towards cheaper comparator options.

In combination, these factors mean that manufacturers must consider the appropriateness of their clinical trials for reimbursement even earlier, in order to avoid later challenges. But the principles and requirements of what evidence is required is no different to other ATMPs for each country, and potential indication.

Activities for Manufacturers to Consider Include:

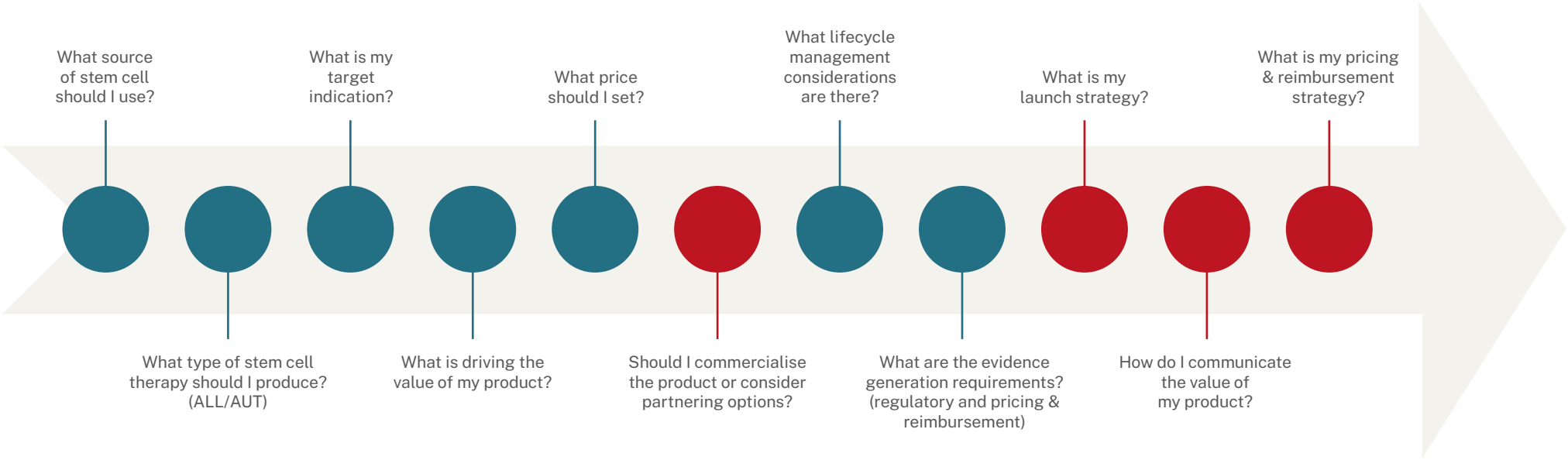
- Early Economic Modelling
- Evidence Gap Analysis
- Analogue Analysis

DISCUSSION

Cell therapies are a complex and heterogeneous group of therapies which are difficult to define. For the purpose of this whitepaper, we have focused on regenerative stem cell therapeutics.

It is clear that there are market access challenges facing all manufacturers in the early stages of product development, but those can be even more acute when developing an innovative therapy. Manufacturers of stem cell therapies will face many decision points along the way (Figure 5).

Figure 5: Example of manufacturer considerations and decision points throughout a stem cell therapy asset's lifecycle



Throughout this whitepaper, we have highlighted the following key pieces of advice in the pre-launch stages of development:

TARGETING:

It is important to clearly define the product, both in terms of source of materials and the target product profile. A key decision in the development of stem cell products is the choice of target therapy area.

There is a great market potential for these therapeutics, particularly given the potential of stem cells to differentiate into many cell types. Stem cell can be used to develop therapeutics in a broad range of disease areas, as evidenced by Phase 2 clinical trials in over 10 different therapy areas.

Current trends suggest that stem cell therapies will emerge in neurology, immunology and cardiovascular indications. Understanding how this competitive pipeline may change over time could be beneficial to aspiring manufacturers.

INTERACTIONS BETWEEN COST, VALUE AND PRICE:

There is an opportunity for allogeneic stem cell therapeutics to take advantage of economy of scale to reduce manufacturing costs and make a wider range of indications and disease areas commercially feasible. This could see some targeting high volume and prevalent conditions.

The key driver for the achieving this market growth is achieving sufficient price levels, which will be determined by clinically relevant outcomes, and evidence to support value and cost effectiveness within the HTA and reimbursement processes. One key question on the cost side, is how low can manufacturing costs go for a successful product – this lower threshold will likely determine which indications could remain not worth targeting.

Autologous stem cell therapies will remain niched in high priced, large unmet need targets.

Other things to consider:

There are a number of other elements to consider, including:

- Decision-making around whether to commercialise without support or partner with other companies or funding sources.
- Tools to support the communication of product value.
- Launch sequencing and pricing & reimbursement strategies.

MARKET TRENDS:

In addition, there are market access trends to consider during the pre-commercialisation stage, which could create barriers to entry further along the product journey.

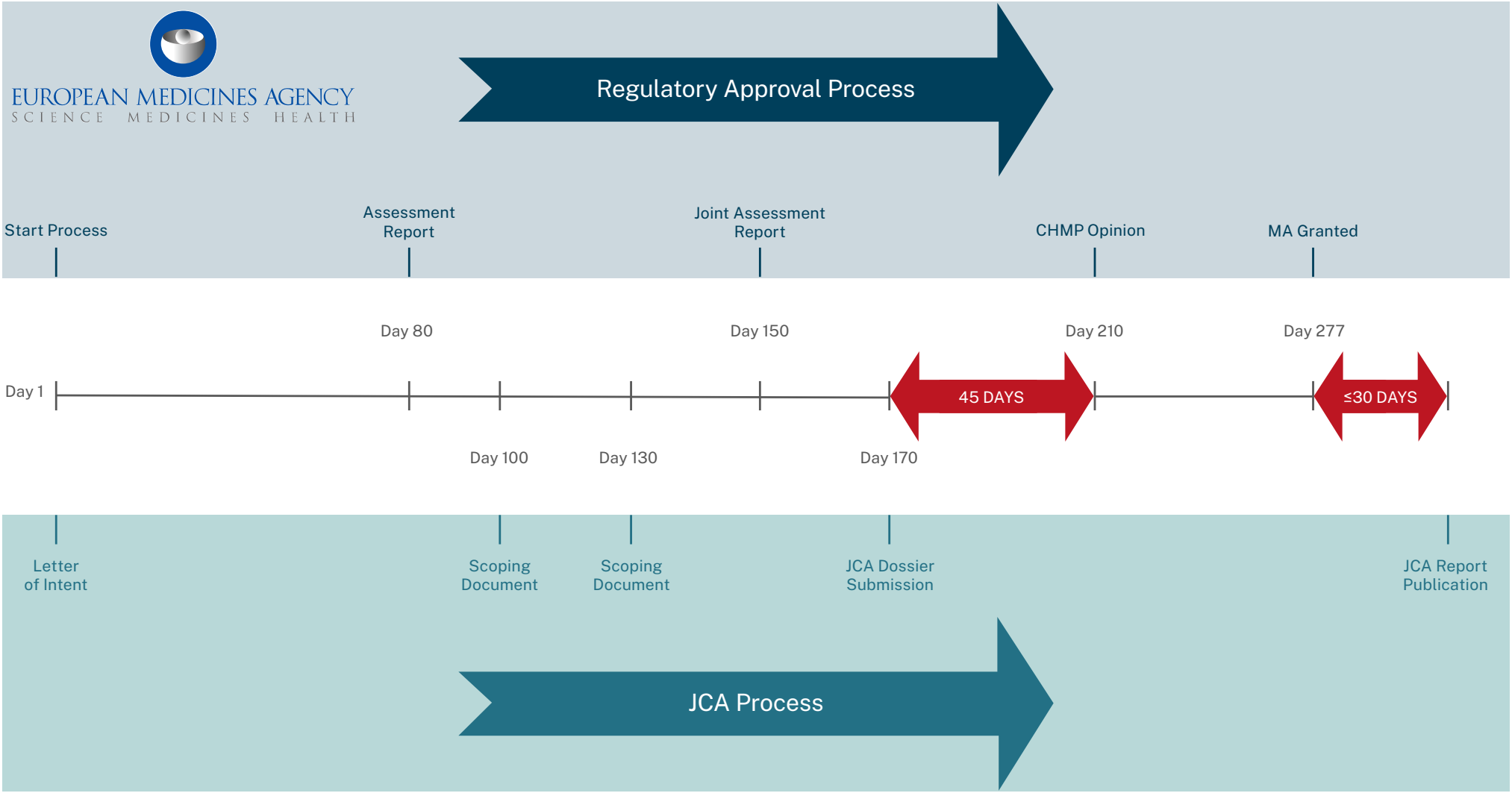
Example: The emergence of EU Joint Clinical Assessment (JCA)

The European Union has announced a centralised joint clinical assessment of medicinal therapies to be undergone in parallel with the market regulatory authorisation. The objective of this process is to identify the added therapeutic value of new health technologies in comparison with other existing health technologies in a centralised manner, in an attempt to help ensure patient access across the EU.

Starting in January 2025 all new oncology and advanced therapy medicinal products (ATMPs), stem cell therapies are included in the latter, will undergo the centralised EU JCA process (Figure 6).

Multiple uncertainties remain around the JCA implementation, but the immediate impact on the EU market strategy has to do with the timelines of the new process. The new process requires the manufacturer to have the market access strategy completed at least 1 year earlier, previously the health technology assessment started following the regulatory approval, however with the new process both start in parallel (Figure 6).

Figure 6: New JCA process timelines in the European union



Source: EUnetHTA website (Ref 19).[9]

Manufacturers should consider the impact of the new timelines. Currently manufacturers, after submitting for regulatory review, are able to continue generating additional evidence to support the health technology assessment at a country level. With the new JCA process, manufacturers are required to have all the data to support health technology assessment at the time of the regulatory submission.

Additionally, it is likely that the largest EU countries (Germany, France, Italy and Spain) will continue performing a national clinical assessment process, therefore there is a risk that the total market access timelines are delayed from the current ones.

KEY RECOMMENDATION FOR MANUFACTURERS

Our key recommendation for manufacturers is to **start planning their market access and HEOR strategy early**. This is especially relevant in stem cell therapeutics given the considerations of this market as highlighted in this whitepaper.

Even at a pre-clinical stage we would recommend:

- Understanding the competitive landscape and likely comparators (landscape assessment).
- Understanding the relative risks and returns of each potential target indication (Commercial attractiveness matrix).
- Understanding volume potential (and sub populations, areas of greater need) (Opportunity assessment, including forecast modelling).
- Refining and considering the different target product profiles (TPPs) and what drives value (TPP development).
- Understanding key evidence requirements, and key uncertainties/evidence gap that would need to be addressed pre- or post- launch (early economic modelling).
- Understanding price potential across key markets (payer research and analogues assessment).
- Multidisciplinary decision making and matrices (market access strategy).

By considering the value-based framework, HEOR and lifecycle management early in the product development, manufacturers should identify potential challenges and have time to adjust their market access, clinical or data gathering strategies to maximise the product opportunity.

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ABOUT US

Cogentia was founded in 2010 with our head office located in Cambridge, UK. Since then, our company has worked with a wide range of pharma and biotech clients, recognising the importance of market access support throughout early product development through to in-market support.

We have a proud history of providing original thinking, insightful advice and full alignment with each client's product and project to deliver quality outputs on time.

We offer an integrated team of market access experts – with skills in both technical disciplines such as economic evaluation, health technology assessment, evidence synthesis and also in strategic aspects of market access such as value proposition development, payer research and global value dossiers.

Cogentia teams work in close partnership with our clients - often on long term engagements - ensuring alignment with project requirements, driving clear communication and optimal outcomes.

Cogentia specializes in market access, offering a full range of services including:

- Value Proposition Development
- Pricing research
- Market Access Strategy
- Valuation and Sales Forecasts
- Economic Evaluation
- Evidence Synthesis
- Health Technology Assessment (HTA)
- Stakeholder Engagement

Cogentia®

CONTACT

enquiries@cogentia.co.uk
cogentia.co.uk

Cogentia
22 Station Road,
Cambridge CB1 2JD,
United Kingdom