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How To Run Successful Clinical Trials In Japan

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There is no longer any excuse not to include Japan as an integral part of any global clinical-development program for either pharmaceuticals or medical devices. With a more receptive climate for both starting and running trials, an improved infrastructure for clinical research, and significant advances in accelerating drug approvals, Japan is now firmly on the global development map.

There have always been strong reasons to secure a foothold in Japan. It is the world's third-largest single pharmaceutical market after the US and China – or second-largest for prescription drugs – with a rapidly aging population (26.6% over 65 years old in 2016) increasing the demand for healthcare and medicines.

Other compelling reasons to always involve Japan in global drug development include: a mature local market; a renewing economy; the regulatory flexibility around Japanese data in global clinical-trial packages; an extensive, nationally-funded healthcare infrastructure with universal health insurance; a large and adherent patient population; and a strong emphasis on quality and precision in clinical research.

Japan's attractiveness for the inward investment proposition for the pharmaceutical sector has further increased in recent years as the Japanese regulatory authorities have made concerted efforts to align drug approval timelines with the US and Europe. The situation in Japan today is a far cry from before, when Japanese patients had access to new medicines five to ten years after their counterparts in the US or Europe.

More specifically, Japanese authorities have created new incentives including, but not limited to, priority- or conditional-approval programs for new medicines in areas of high unmet need such as orphan diseases. Additionally, the regulatory agency has removed some significant regulatory or bureaucratic obstacles for clinical trials, such as past reluctance to consider foreign study data and reliance on bridging studies over full participation in clinical development worldwide.

Nonetheless, the complexities of planning and running clinical trials in Japan can be daunting for the uninitiated. Tapping into local expertise and resources that help non-nationals to navigate the regulatory hurdles, make the right connections and home in on eligible trial participants can ease the process.

Regulatory And Operating Environment Changes

In a recent interview with Informa Pharma intelligence, Toru Fujieda, Hiroshi Yamada and Toshitaka Kawaratani, respectively President, Vice President and Head of the Consulting Division at CMIC Co., Ltd, a pioneering Tokyo-based contract research organization, highlighted how the regulatory and operating environment for clinical trials in Japan has markedly improved in the past decade.

Improvements include much shorter review times for new drug applications (NDAs). In 2007-08, for example, the average time taken to assess and approve a NDA in Japan was 1.5 to 3 years. In the US and Europe, the average drug-approval time was about two years. Now drugs are being approved in one year or less in Japan, setting a faster pace than both the FDA and the EMA, Kawaratani notes "The regulatory authority has recognized that in approval timings for product launches, we need to be competitive with other countries such as the US and European markets," he adds.

Along the way, the Japanese government and the Pharmaceutical and Medical Devices Agency (PMDA) have introduced incentives such as a 10-20% 'Japan-first' pricing premium for medicines developed locally in parallel with other major markets, or expedited approvals for rare-disease and other medically significant drugs.

Price premiums are available under the orphan drug designation, launched around three years ago and now applying to 20-25 projects annually. For truly innovative medicines, price premiums can range from 70-120%.

Special provisions were also created for the review and approval of gene and cell therapies in Japan. The Sakigake pathway for breakthrough and regenerative medicines includes substantial regulatory and scientific support for development plans, rolling NDA submissions and an accelerated review period.

Aggressive recruitment and training strategies were introduced at the PMDA, nearly doubling its review staff. In addition, Kawaratani points out, the agency has adopted a more consultative approach in its relations with the pharmaceutical industry. Both the frequency and quality of communications have improved in both directions, as the PMDA commits determinedly to a strategy of

innovation. That includes closer communications with regulatory counterparts overseas, such as the FDA and the EMA, as well as more global alignment through the International Conference on Harmonization (ICH).

More Flexible Conditions For Clinical Trials

The PMDA's innovative stance has created more flexible conditions for Japanese clinical trials. Rather than asking routinely for large studies in the local population, the PMDA now requires data from only a certain proportion (and sometimes a limited number) of Japanese patients to confirm drug efficacy and safety.

PMDA's increased recourse to term-restricted conditional approvals, supplemented by real-world data post-launch, for innovative medicines in areas of high unmet need is also helping to cut clinical development times.

With the liberalization throughout the drug development and registration process, "many global ventures now want to come into the market to aim for the first launch in Japan", Kawaratani says. That aligns very much with Japan's interest in promoting itself as a viable destination for global clinical trials.

Over the last 10 years there has been a growing trend for programs either to include Japanese sites in their trial protocols or to incorporate bridging studies from Asian countries such as Korea and/or Taiwan. As a result, 50-60% of clinical trials now con-ducted in Japan are associated with global programs.

Scheduling Clinical Trials In Japan

In parallel, clinical trial start-up times in Japan have improved significantly. "Around 10 years ago it took around five or six months for site initiation," Yamada mentions. "The current situation in Japan is that it takes three or four months on average."

More efficient study initiation reflects the availability of an extensive infrastructure for clinical trials. "Many public or university hospitals have a very good system in place for clinical trials," Fujieda points out. "It's very easy to conduct trials nowadays." Government efforts to promote a better co-ordinated clinical-trial environment through hubs and networks have further underpinned the infrastructure.

Better resourcing for local trials has also made an impact. Many investigator sites can now call on clinical research coordinators (CRCs) with a full range of capabilities to support trial initiation and implementation.

CMIC launched not only Japan's first CRO but also its first site management organisation (SMO). The group's in-house SMO, Site Support Institute, has partnerships with medical institutes and university hospitals extending from Hokkaido to Okinawa, the northernmost region to the southernmost region of Japan. This extensive geographic coverage enables local CRCs to have an important part in identifying both the right sites and the right patients for specific trials.

Joint ethics-committee reviews for smaller local trial sites are also well established. In the past, one of the hurdles to getting clinical trials up and running in Japan was the need for most sites to have their own institutional review board.

"The time needed for selection and screening [study participants], everything is running more smoothly than 10 years ago," Kawaratani notes.

GCP Harmonization And SOPs

Touching all bases from first patient in to last patient out, the mechanisms and provisions for running clinical trials in Japan are increasingly harmonized with global standards, Kawaratani emphasizes.

That also goes for Good Clinical Practice (GCP). Despite legislation bringing the country into line with ICH GCP standards in 1997, Japan's rigorous and conservative application had traditionally been a disincentive to clinical-trial notifications. Additionally, other areas of difficulty included the obtainment of informed consent from trial participants who culturally tend to defer to medical professionals and may not welcome a full discussion of their condition with a clinical investigator; and the requirement for chief investigators at each study site to personally supervise financial arrangements and all other aspects of trial conduct. Now, information-sharing and communications with site heads are more fluid and systematic and so are speeding up clinical research approval and monitoring procedures.

Very often global CROs operating in Japan use their own SOPs when applying GCP to clinical trials. CMIC has no problem conducting trials in accordance with ICH GCP, but CMIC can also use client's SOPs. Clinical Research Associates (CRAs) working for CMIC are well trained in both the CRO's standard operating procedures and those of its clients.

Investigator, Patient Commitment To Clinical Trials

While 10-20 years ago hospitals were often reluctant to get involved in clinical trials owing to the perceived

administrative and other burdens, with little prestige attached to clinical research among healthcare professionals and academics, and a paucity of financial or other incentives, to act as clinical investigators, that has now changed, according to Fujieda. Today, with a stream of cutting-edge therapies emerging from research and development pipelines in key areas such as oncology, physicians are more motivated to participate as a means to widen patient access to new medicines.

Despite the availability of universal healthcare coverage in Japan, a similar rationale also drives patient interest in clinical trials, particularly with non-responders to existing therapies for cancer or other critical conditions. Transportation-fee support for clinical-trial site visits, and the opportunity for detailed consultations with physicians as well as access to new treatments, may also encourage patient involvement.

Moreover, the cultural deference to healthcare professionals makes these patients more likely than their counterparts in other countries to adhere strictly to study protocols.

Managing Clinical Trial Costs

One disadvantage to running trials in Japan could be that costs tend to be higher than in other markets, a disparity blamed on various factors such as slow patient recruitment, the necessity for face-to-face communication between the investigators and CRCs, or the complexity of study payment systems.

Site costs can be high, with each trial site employing its own fee system and calculations for different trial components such as principal investigators, clinical research coordinators or indirect costs.

Fee negotiations need to be conducted with site staff, rather than principal investigators as in other markets. While some clinical-trial costs are covered by national health insurance, the sponsor is held responsible for other costs (e.g., laboratory tests, imaging, comparator drugs).

While CMIC tries to keep costs down, they can be complicated by the trend of client requirements such as 100% verification of all source data in Japan. On the upside, this attention to detail pays off in terms of the data quality, given the highly professional attitude of investigators in Japan and their patients' seriousness about following study protocols and reporting requirements to the letter.

Companies bringing clinical trials to Japan can also take advantage of the PMDA's in-creased openness to data from comparable Asian countries, such as South Korea, Taiwan and Singapore to recommend Asian trials including the Japanese population. They can leverage these other markets to generate an Asia data package that balances the higher costs of running trials in Japan, when US/EU trials are completed in advance.

Usually, these combined packages depend on protocol design and drug indication of interest, Yamada notes. Clinical-trial sites in other Asian countries must also be 100% GCP-compliant, as the PMDA will directly audit sites abroad where necessary.

At the same time, regulatory conditions still require some level of Phase I, II or III data to account for potential variations in the Japanese population, with pharmacokinetic data depending on the specific compound and indication. This proportion is currently around 15%, depending on the indication and protocol design.

Moreover, the PMDA no longer recommends bridging studies as a means of accessing the Japanese market. It would rather see global clinical trials that take in the Japanese population.

Overcoming Drug Lag

Most pharmaceutical multinationals start their global trial programs in either the US or Europe and will wait until Phase II studies are started in those markets before initiating Phase I development in Japan. However, some global giants and Japanese companies, developing medicines globally, do start with clinical trials in Japan. As Yamada points out, global clinical trials still tend to be slow at adding Japanese patients to the global program, due to the higher cost of running studies in Japan as well as traditional barriers such as unfamiliarity with Japanese language, culture or clinical-trial processes.

There are exceptions, nonetheless: companies may be encouraged to start global trials in the Japanese population in indications, such as gastric cancer, which are a high unmet need. Accelerated-approval provisions for oncology therapies may provide further leverage.

Japan's greater reliance on surrogate endpoints as a basis for drug approvals in some conditions is potentially attractive. In diabetes mellitus, for example, the primary endpoint is reduction in glucose levels or HbA1c (glycated haemoglobin) rather than broader outcomes such as death rates.

Finding The Right Patients

While patients are available and willing to enrol in clinical trials in Japan, it can be difficult making people aware of opportunities to participate and finding exactly the right patient cohort for a particular study.
As Akihisa Mitake, President of CMIC's Site Support Institute Co., Ltd., and Shinichi Kei-no, President of CMIC Healthcare Co., Ltd., noted in a separate interview with Informa Pharma Intelligence, in the 10 year plus the CMIC group has been involved in patient recruitment,, approaches to enrolling patients have evolved in line with the shift in the marketplace and companies' research and development pipelines from chronic diseases towards more complex conditions such as rare diseases, difficult-to-treat cancers or central nervous-system (CNS) disorders.

This shift has boosted demand for specialist patient recruitment organisations (PROs) and more targeted recruitment strategies away from traditional reliance on print media or the internet. These strategies may be hampered by the difficulty of obtaining detailed information on relevant trials from public websites such as ClinicalTrials.gov.

"Even if they find the right information, they cannot directly access the clinical-trial sites for more information," Keino comments. Moreover, participating study sites may be reluctant to disclose details such as the names of hospitals involved in a trial.

Against this backdrop, CMIC is developing new initiatives tailored to patient recruitment in the fast-growing oncology market. These include setting up an online portal for cancer trials that would act as a go-between by screening eligible patients and referring them to trial sites.

CMIC is also working with ReasonWhy Inc., an internet-based company offering second opinions on medical diagnoses through a system called Findme, on disseminating oncology-trial information to patients.

Another initiative involves partnering with life assurance companies enabling CMIC to provide information on available clinical trials to newly diagnosed cancer patients. Emphasis is on having a flexible approach to patient recruitment and a customized alternative to one-size-fits-all strategies, where the primary focus is on trial registration panels, Keino explains.

Recruitment techniques can be modified according to age, gender and target disease. For example, an analog approach may still be suitable and effective for older people unfamiliar with, or little interested in, digital media.

Partnerships For Patient Recruitment

CMIC's strength in having patient recruitment as a group function lies in its broad range of partnerships, which also includes pharmacies, companies that process prescription receipts, organizations providing regular medical check-ups, and nursing-care specialists. All of these are potential channels of communication with patients who may wish to take part in clinical trials.

Medical- and prescription-claims databases provide another means of identifying eligible patient pools through recorded prescriptions and diagnoses, or of assessing site feasibility for clinical studies.

In-market specialists such as CMIC can also help a study run smoothly by taking a meticulous approach to patient awareness and informed consent, or ensuring that any devices used in a trial, such as electronic patient diaries, are user-friendly and fully connected.

As Mitake observes, Japanese people expect their devices to work, and something as simple as using foreign batteries with the wrong voltage for Japan can undermine confidence and trust if it interferes with device functionality.

Continuing Challenges

Despite the many improvements in the Japanese clinical-trial environment, challenges, such as slow progress with access to electronic medical records, patient consent for secondary data use and integration of Japanese clinical-trial data into global databases, remain.

Such challenges can be particularly taxing for small- to medium-sized pharmaceutical companies and bioventures without experienced international staff. In the absence of a Japanese subsidiary able to conduct clinical trials under local GCP requirements, such companies must appoint an in-country clinical caretaker (ICCC) that can jointly assume their legal, regulatory and operational obligations.

Indeed, an ICCC-licensed service provider is the crucial bridge between an overseas company and the PMDA as well as clinical-trial sites. Third parties can open doors in contract negotiations with study sites, as well as reconcile different contract formats for individual sites.

It can also act as a go-between with the PMDA, which welcomes early consultation – whether formally or informally – on clinical-trial designs and data specifications. Japan has very specific requirements for post-marketing surveillance (PMS), with a particular focus

on risk management during the first six months after launch, and strict monitoring requirements in specialist areas such as rare diseases.
All interactions with the PMDA need to be in Japanese, as do most interactions will clinical researchers. Indeed, a strong, traditionally insular national culture pervades all aspects of the business and regulatory environment in Japan, which to outsiders can sometimes appear opaque. Consequently, a local partner can make a huge difference in breaking down any communication barriers.

Disconnecting Development

Companies looking to conduct clinical trials in Japan should be thinking about disconnecting drug development from commercial activities, such as business partnering, so that their development program runs simultaneously in Japan and other key markets such as the US and Europe.

That way, they can take full and early advantage of the new wave of regulatory liberalization in Japan and a growing pharmaceutical and healthcare market geared to innovation. Teaming up with the right partner will go a long way towards ensuring this experience is a positive one.

CMIC is Japan's largest CRO, with more than 25 years' experience, 1,200 clinical re-search associates, over 140 consultants and medical writers, and services ranging from contract-development-and-manufacturing (CDMO), preclinical, and clinical-trial support through to regulatory consultation, PMS and pricing consultation for negotiations with the Ministry of Health, Labour and Welfare (MHLW).

Pharmaceutical Value Creator

This broad range of services underpins CMIC's unique 'Pharmaceutical Value Creator' business model. With so many varied inputs from different areas of the business, the group has prompt access to large volumes of valuable information on pharmaceutical-market trends. This enables CMIC not only to expand the scope of its business but to provide considerable added value to its industry clients.

Given the growing encouragement for Asia data packages to support global clinical trial programs and product approvals in Japan, CMIC is also well placed as the leading pharmaceutical-services provider across Asia, with headquarters in Japan and operations in China, Korea, Taiwan, Hong Kong, Singapore, Malaysia, Thailand, Vietnam and other countries in the region.

With expertise in key therapeutic areas such as oncology, cardiovascular disease, CNS disorders and regenerative medicine, as well as medical devices and gene or cell therapies, CMIC can be an invaluable partner for companies ready to give a more outward-facing Japan the parity of recognition it now deserves in global drug development.

ACT NOW – Cancer Trials At The Leading Edge

Thought Leadership in Association with ICON

Adoptive Cellular Transfer (ACT): Novel Cancer Trials Demand That Participating Sites Act Differently

In the past five years the evolution of adoptive cellular transfer (ACT) for the treatment of lymphoma, leukaemia and myeloma patients has grown exponentially as the efficacy and specificity of these treatments offer curative promise , creating new hope for patients. With European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvals of Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) autologous CAR T therapies, ACT is moving towards the frontline setting, expanding the clinician's armamentarium of cellular cancer treatments. High cost remains a concern but the explosion of commercial companies exploring allogeneic, polycistronic, switchable constructs and novel local manufacturing approaches is likely to reduce future costs, whether through competitive pressure and/or technological advances. Access to ACT therapies will broaden globally, engaging smaller community settings. The successful development of cell therapies is dependent on the growing number of academic medical or hospital centres which are able and willing to participate in clinical trials. Until now, the expertise has resided in larger specialised haematology centres in the US, Europe and China. However, with more technologies come more trials, and solid tumour interests are increasingly penetrating the field.

As more pharma and biotech companies bring their ACT platforms to the clinic, there is a need for the assistance of clinical research organisations (CROs) to support the con duct of clinical trials. Valued for their relationships with trial centres, CROs have been thrust into the forefront of operationalising ACT studies. So what can sites expect and commit to when participating in ACT trials? Based on our CRO experience, there are four areas of focus: Regulatory, Logistical, Patient Safety and Data Management.

Regulatory knowledge is paramount. ACT studies are classified in the genetically modified organism (GMO) category, which has bespoke requirements. In many countries, applications must be submitted to specialised local and/or national agencies. Additional time for the regulatory set-up period should be anticipated and it is essential to have a team on hand that is familiar with navigating GMO regulations, as these regulations are constantly evolving. For example, the US National Institutes of Health (NIH) is re-evaluating gene therapy oversight to eliminate duplicate reporting. In large academic centres, regulatory expert groups are well established. How-ever, as competition for ACT studies grows, and established centres of excellence experience resource constraints within their own regulatory groups, there will be an evolving drive and opportunity for community hospitals to engage in ACT clinical development. These institutions will need to equip themselves with regulatory expertise. Another perspective is that even in the centres where ACT is established, it has been focused in the haematology-oncology divisions. With the advent of new therapeutic targets against sarcomas and other solid tumours, oncology departments will need to familiarise themselves with information that may already be resident elsewhere within their own hospitals.

The intensive and demanding logistics of conducting ACT trials necessitates a high degree of organisation within institutions and sophisticated inter-departmental cooperation. Apheresis is a core component of autologous ACT requiring the engagement of transplant units at the centre of the process, including lymphodepletion and infusion of cells. Apheresis unit/materials and transplant unit audits are mandatory practices in an ACT clinical trial. Each commercial sponsor is likely to have its own audit requirements. So transplant units working on multiple studies for different pharmaceutical companies should be prepared to entertain many audits. Standardisation or universal accreditation of ACT studies remains an aspiration. Sites that have revised their infrastructure to meet demands of ACT have been the most successful in conducting studies. For emerging allogeneic approaches, apheresis is not part of the treatment paradigm but transplant units remain pivotal with their role in lymphodepletion and T-cell infusion. In autologous approaches, the chain of identity which ensures a patient receives their own cells post-modification requires careful coordination through form filling and registration. This is no small feat of resource management. Patient scheduling is also a sensitive matter as with autologous therapies, there are manufacturing scale capacity and limitations at facilities where cells are modified via viral

vectors, plasmids, transposons, etc. Managing site and patient expectations is a key factor as well as scheduling the patient treatment pathway across the various clinical care teams. Larger academic institutions have established specialised ACT units that specialise in cellular therapy studies.
The positive results with ACT come with concomitant safety risks that require skilled patient management. Sites require robust standard operating procedures (SOPs) specific to ACT-related adverse events. During the acute infusion phase, the inpatient setting provides good access to health care experts in the supervision of the greatest potential risks such as cytokine release syndrome, neurotoxicity or graft versus host disease (GVHD; allogeneic approaches). However, once the patient is discharged, a dedicated line of communication for them is recommended, as well as immediate proximity to skilled urgent care.

ACT studies generate large amounts of data over a short period of the treatment cycle including laboratory, other safety data, prior treatments and concomitant medications – these patients have multiple lines of prior therapy. As such, robust, validated electronic medical record systems are required. Data quality and currency become a challenge with the large volumes of data, estimated to be up to 10 times that observed in other oncology studies. The site's data coordinators must have sufficient time to enter data expeditiously as sponsor companies and regulators are constantly looking for updated safety information. Considering the numerous and still evolving risks of ACT therapies, the importance of data currency cannot be understated.

ACT will continue to make significant inroads into both haematological and solid malignancies with increasingly sophisticated and diverse cell constructs. Whilst the good news is that this is providing increased access for patients to treatments across a broader swath of health care facilities, there is also increased competition for study site re-sources. Being prepared with regulatory intelligence, scalable logistics, resource commitments, as well as dedicated patient safety and data management teams will present challenges that surpass those of other oncology clinical trials. This is life at the leading edge.

Stem Cell Research Progress In The US: Where Are We Now?

Thought Leadership In Association With Syneos Health

Executive Summary

The history of stem cell research has been marked by a combination of great promise, disappointment and controversy. But progress is being made, with a number of stem cell therapies approved and many more in the late-stage pipeline. While the US has lagged behind other regions in stem cell therapy approvals, recent developments on the regulatory front are intended to provide a clearer path forward and accelerate development.

The history of stem cell research has been marked by a combination of great promise, disappointment and controversy. But progress is being made, with a number of stem cell therapies approved and many more in the late-stage pipeline. While the US has lagged behind other regions in stem cell therapy approvals, recent developments on the regulatory front are intended to provide a clearer path forward and accelerate development. Looking at marketed stem cell therapies and those in development, there are trends emerging in the US that are influencing stem cell R&D and deal-making. While the outlook for stem cell therapies is improving, unique commercialization challenges remain that developers should consider early in the clinical development process if they are to succeed in gaining marketplace access and adoption.

Stem Cell Types – Where The Action Is

There are two major groups of stem cells – embryonic and non-embryonic. Embryonic stem cells (ESCs) are derived from three-to-five-day-old embryos and hold the most potential as they can be used to regenerate any cell type. However, both ethical and safety concerns have restricted ESC therapeutic development. While no ESC therapy is currently on the market, several companies have been successful in early-stage clinical trials for the treatment of macular degenerative conditions. Other indications where ESCs are being explored include type 1 diabetes, amyotrophic lateral sclerosis (ALS), Parkinson's disease and spinal cord injury.

Adult stem cells – including mesenchymal stem cells (MSCs) and blood-forming hematopoietic stem cells – are found in small numbers in some adult tissues, such as bone marrow or fat. Compared with ESCs, adult stem cells are more limited in their ability to regenerate other cells. Despite this, their use in the treatment of disease has been much more successful, as exemplified by the widespread use of bone marrow transplants where a patient's own (autologous) cells or a donor's (allogenic) cells are transplanted into the patient to treat diseases such as blood cancers.

The majority of ongoing stem cell trials use MSCs. These cells can be isolated from bone marrow and other tissues such as adipose tissue, umbilical cord tissue and placental cells. They are amenable to in vitro expansion and can differentiate into osteoblasts, chondrocytes and adipocytes. As of 2016, there were over 490 clinical trials using both allogenic and autologous MSCs; key disease areas include graft versus host disease (GvHD), cardiovascular diseases, bone and cartilage disorders, immunological conditions and neurological diseases. The world's first marketed stem cell therapy using MSCs – Prochymal (remestemcel-L) developed by Osiris Therapeutics (later acquired by Mesoblast Ltd.) – was approved in Canada in 2012 for the treatment of acute GvHD in children, the leading cause of transplant-related mortality.

Induced pluripotent stem cells (iPSCs) are generated from adult cells by overexpression of certain transcription factors, which make the cells similar to embryonic cells at a cellular level. These cells were once thought to offer great potential for therapeutic applications but clinical development has proven challenging. Despite numerous setbacks, some clinical development is ongoing, and international academic and commercial groups have reported encouraging results in age-related macular degeneration (AMD) and GvHD.

US Is Late To Game

Historically, there have been more stem cell products approved in other geographies compared with the US. Notable products that have been approved outside the US include Holoclar (approved in the EU for cornea damage), Neuronata-R inj. (autologous MB-MSC; approved in South Korea for ALS) and Alofisel/Cx601 (darvadstrocel; approved in the EU for gastrointestinal fistula). Recent clinical trial successes owe to the advantages associated with using allogenic products, targeting of indications with high unmet need, and improved clinical trial design

and endpoint selection. There has also been significant development in cell type identification/selection and preparation technologies that are critical for successful stem cell product development.

However, overall progress in the stem cell field has been slow due to a number of obstacles, including complex administration and special handling requirements, requirements for "hard" clinical trial endpoints for certain indications and hurdles to ethics committee approval.

Stem cell therapy development in the US faces additional challenges. The only FDA-approved stem cell therapy products to date are limited to hematopoietic progenitor cells derived from cord blood (see Exhibit 1). According to a survey of academic cardiologists/interventional cardiologists, ophthalmologists and rheumatologists conducted by Syneos Health (SERMO RealTime platform, conducted June 2018), key reasons for the lack of stem cell product approvals in the US include insufficient government support and more stringent FDA requirements for trial design and approval compared with other regions. However, recent updates to the regulatory process in the US hold promise for accelerating development and commercialization of stem cell therapies going forward.

Exhibit 1. Currently Approved Products In The US

Product	Manufacturer	Product Description	Indication
Allocord	SSM Cardinal Glennon Children's Medical Center	Hematopoietic progenitor cell from Cord Blood	*Unrelated donor transplantation in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment*
Clevecord	Cleveland Cord Blood Center		
Hemacord	New York Blood Center		
Ducord	Duke University School of Medicine		
HPC Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank		
HPC Cord Blood	LifeSouth Community Blood Centers, Inc.		
HPC Cord Blood	Bloodworks		
	MacoProductions S.A.S.	Sterile Cord Blood Collection Unit with Anticoagulant	Collection of 40 – 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section

**Includes only stem cell products, not including cell therapy products (e.g., cultured fibroblasts for dermal applications) or gene therapy products*

Regulatory Guidance Catching Up

The creation of the breakthrough designation for products treating serious or life-threatening diseases may allow the US to catch up over time by providing increased FDA guidance and potentially accelerated review for appropriate products. Kite's CAR-T approval is a recent example of how this program can be leveraged to accelerate development.

In addition, the 21st Century Cures Act, enacted in December 2016, provides additional funding for stem cell research and requires the FDA to facilitate an efficient development program for, and expedited review of, new medicines meeting the definition of a regenerative advanced therapy – now referred to as the Regenerative Medicine Advanced Therapy (RMAT) designation. RMAT designation gives the sponsor of a new drug access to increased meeting opportunities with the FDA, in a

manner comparable to those offered to sponsors of breakthrough-designated therapies. The RMAT designation may require a lower clinical evidence burden to obtain than the breakthrough therapy designation, though this awaits clarification. Furthermore, RMAT designees acquire the ability to incorporate real-world evidence (RWE) and potentially other non-traditional approaches into the approval process. However, it remains to be seen whether this initiative will achieve its goal of facilitating faster development while maintaining safety and efficacy standards. In addition, the FDA has promised to revise their guidance on regenerative medicines sometime in 2018 to keep up with and parallel advances in stem cell research technologies and innovation.

Promising Near-Term Pipeline – And Bump In Deal-Making

The near-term pipeline for stem cell therapies in the US looks promising, with a number of products in Phase II and above, including remestemcel-L (Mesoblast), which is preparing to file a BLA for acute GvHD. Other key areas of focus for stem cell therapies being developed in the US are cardiovascular and immunotherapy indications (see Exhibit 2).

Exhibit 2. Stem Cell Pipeline In The US

Indication Category	Product	Company	Lead Indication	Current Phase
Immunology	Habeo Cell Therapy	Cytori	Hand Scleroderma	III
	MSC-100-IV/remestemcel-L	Mesoblast	Acute GvHD (Pediatric)	BLA Filing Underway
	MPC-300-IV	Mesoblast	Chronic inflammatory conditions	II
Cardiovascular	ALD-301	Nuo Therapeutics/ Aldagen	Peripheral Artery Disease	II
	C-Cure	Celyad	Heart Failure	III
	Ixmyelocel-T	Vericel	Dilated Cardiomyopathy	II
	MyoCell	U.S. Stem Cell	Heart Failure	III
	Stemedyne-MSC	Stemedica	Ischemic Stroke, CHF	II
	MPC-150-IM	Mesoblast	Chronic congestive heart failure	III
Endocrine	PDA-002 Cenplacel	Celgene	Diabetic Neuropathy, Diabetic Foot Ulcer With and Without Peripheral Arterial Disease	II
Musculoskeletal	ECCO-50	Cytori	Osteoarthritis	II
	MPC-06-ID/Rexlemestrocel-L	Mesoblast	Chronic low back pain	III
Sensory Organs	MA09-hRPE Cellular Therapy	Astellas	Dry AMD, Stargardt's macular degeneration	II
	ReN003	ReNeuron	Retinitis Pigmentosa	II
	jCell	jCyte	Retinitis Pigmentosa	II

There have been 11 acquisition deals completed in the US over the last few years, with over $1.5bn in total deal value since 2015. Notable deals in 2017 included Astellas Pharma's acquisition of Universal Cells for up to $102.5m in up-front and milestone payments; the acquisition of Calimmune by CSL's CSL Behring unit for $91m up front and up to $325m in milestones; and BioTime's purchase of 21% of Cell Cure Neurosciences' shares from Hadasit for $12.4m. Although ex-US, Takeda's $628m acquisition of TiGenix, which closed in June 2018, is a major event in the stem cell research world, signaling Takeda's high level of interest in the stem cell space. Takeda hopes to leverage TiGenix's expertise to accelerate development of novel stem cell therapies, including Cx601 for the treatment of complex perianal fistulas in Crohn's disease.

Preparing For Commercialization

As stem cell therapies start to clear development and regulatory hurdles in greater numbers, interest among treating physicians and patients is certain to be high but that alone is unlikely to guarantee commercial success. Awareness of stem cell products in development is already high in therapeutic areas where stem cell therapies are likely to launch, as 78% of ophthalmologists, 56% of cardiologists, and 45% of rheumatologists screened in the Syneos Health survey reported a high degree of stem cell therapy product awareness.

While interest in and awareness of stem cell therapies is high, significant barriers exist to their successful commercialization. A report published by BMC Biotechnology on challenges facing the commercialization of several cell therapies, including stem cell therapies, indicated that postmarket challenges such as manufacturing costs, storage and distribution, reimbursement and convincing providers to change their treatment practices are likely to be key challenges for new entrants. Based on these insights, stem cell product manufacturers should begin planning for these commercialization considerations early in the development process. Results from the Syneos Health survey indicate that journals, conferences and peer-to-peer interactions are important drivers of product awareness in this space. An early focus on physician engagement and education is likely to be key to driving access and adoption.

The development of stem cell therapies in the US has lagged primarily due to widespread clinical failures, limited government investment and a challenging regulatory environment. However, a promising clinical pipeline and an improved regulatory landscape are increasing momentum in the space. As more stem cell products advance into late-stage clinical development in the coming years, researchers and manufacturers would be well-advised to anticipate and address early-on the unique commercialization challenges stem cell therapies present in order to achieve successful product launch. While physicians reported a high level of interest in adopting stem cells (average rating of 6 on a scale of 1 to 7 where 1 = very low interest, 7 = very high interest) in a Syneos Health survey, few were able to recall specific products/trials and most expressed that peer experiences/recommendations along with product efficacy and safety would be the most important factors in their adoption. A structured and comprehensive go-to-market strategy, along with a clear engagement/communication plan, would ensure that key stakeholders understand the product value proposition and how it would address current unmet needs.