ALL BUSINESS DEVELOPMENT
in Life Sciences

report

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subject	**ATMP overview; Market, Business Development, Regulatory & Pricing**

CHINA, JAPAN AND SOUTH KOREA

Content



Executive summary

CHINA

- Large amounts of domestic Chinese funds available for local development.
- Crowded field in certain areas of drug development such as CAR-T, too many players going for the same targets.
- Conditional approval of ATMP:s possible for therapies towards diseases with very high unmet medical needs.
- ICH membership since 2017 has streamlined regulatory process to international standards
- Large number of treatment naïve patients available for clinical trials
- Prices for innovative drugs / therapies often 50% - 90% lower than the West.

JAPAN

- Large interested in Regenerative Medicine the local lingo for ATMPs with nearly all major domestic pharma companies on board such as Astellas, Daiichi Sankyo, Dainippon Sumitomo, Shionogi and Takeda.
- PMDA was the first authority to open up a route for conditional and time-limited approval of ATMPs after explorative Phase 2 studies.
- Priority review and accelerated development through the SAKIGAKE designation system.
- Orphan Drug Designation possible for diseases with less than 50,000 patients in Japan giving 10 years market exclusivity.
- Price level for ATMPs lower than US.

South KOREA

- A large number of ATMPs approved from domestic South Korean companies.
- Scandals are denting the appetite for ATMPs among larger Korean pharma companies with relative developing therapies.
- The latest scandal came earlier this year when Kolon Life Sciences was forced to withdraw and cell therapy product, Invossa, that had been on market for 2 years due to falsified submission. It contained kidney cells, not cartilage cells as specified!
- MFDS has promised increased scrutiny, just as what happened after the great stem-cell scandal in 2006.

1. Introduction

In January 2018, the Swedish Innovation Agency, VINNOVA, awarded SEK48M for five years until December 2023, to establish national support function for Advanced Therapy Medicinal Products (ATMP) called Centre for Advanced Medical Products (CAMP). It is coordinated by Department of Integrated Medical Biology, Umea University. In total there are 25 partners from across Sweden in the project, from academia, and research institutes such as RISE, health care providers, Swedish SMEs such as Idogen and Xintela from Lund, Cell Protect Nordic Pharmaceuticals and NextCell Pharma from Stockholm as well as international ATMP companies operating in Sweden, Cell Seed from Japan and MNC like Novartis.

The goal is that Sweden should become a world leader in developing ATMPs.

Leo Groenewegen, NextCell Pharma and Agneta Edberg, Board member of Idogen, Cell Protect Nordic, etc., are responsible for the development of a global market analysis with a focus on North America, and EU as well as a few countries in Asia, mainland China, Japan and South Korea. as well as email correspondence with Ulf Malmqvist, “Kliniska Studier Sverige – Forum Söder”, at Skånes University Hospital in Lund.

ABD Life sciences Ltd in Hong Kong has been assigned to provide a market overview, focusing on hurdles and requirements covering business conditions, regulatory affairs, clinical development, manufacturing, price and reimbursement etc on a country level.

Some general business advice for all three markets:

- ✪ “Know what you don’t know”.
- ✪ Cultural differences are perhaps the key hurdle in delaying and preventing entry into these markets.
- ✪ Acquisition of the necessary skills and “the knowhow” to survive and prosper is a long-term prospect, for most people/organizations.
- ✪ If these markets are new, then expert on-the-ground support, advice and introductions are almost mandatory to ensure that any business expansion/internationalization plan is achievable.
- ✪ List your Unique Selling Points (USP) and Key Differentiating Factors (KDF), be open, listen and update!
- ✪ Try to obtain the true market demand, never rely on assumptions! Have someone talk to KOLs and patients.
- ✪ Perform regulatory gap-analysis.
- ✪ Develop mitigation plan to handle risks – “Anything could happen”!

- ✪ People are the Key!
- ✪ Establish and build relationships, create mutual trust and understanding, design these for the long term.
- ✪ Preparations, Planning and Allocation of sufficient resources.
  - ⇒ Do not lose technology due to naivety and carelessness.
  - ⇒ Access and use "local expertise" for efficient communication(s), better mutual understanding and the dynamic development of your strategy.
  - ⇒ Be patient and think Long-term!

2. China

This section covers mainland China, excluding Hong Kong, Macau and Taiwan.

2.1. Local ATMP environment

Market sentiments

ATMP is a hot area attracting a lot of investment and activities. However, as always in China there are too many players doing the same thing. There is usually fierce drug development competition for every known target and molecule.

For instance, China has the greatest number of CAR-T projects in clinical development in the world. In October 0218 it was 98 clinical trials (Phase 1 – III) in China with CAR-T type of therapies compared to 49 in US. However, a majority of the Chinese clinical trials are run by academia, with non-GMP produced material citing hospital exemption regulations, which are rising concerns. After a major crack down by the authorities in 2016 after a student died by an unapproved experimental cell immune therapy, the Chinese health authorities in spring of 2019 released now guidelines saying that such experimental therapies would be able to proceed under hospital exceptions at a few selected hospitals. Many in the industry thinks it is actually taking a step backwards and are critical other says new treatments will become available faster than otherwise would be possible. Obviously, there are high risks, something that Chinese entities are well known to be willing to take.

Of course, there are several serious companies involved in CAR-T as well and some are listed further below. The challenge in China is always to pick the ones that are resilient and continue the thrive, not only surviving but also developing into healthy companies. This is a very hot field and there are just too many developing drug candidates towards the same target with very little differentiation between them. Even with the abundant capital resources many will fail. Careful due diligence on any partner is necessary taking into account many aspects that would contribute to business risks.

Actually, the first ever approved gene therapy was in China 2004 when **Shenzhen SiBona Genetech** got approval for its p53 stimulant based on an Adenovirus based

vector carrying a recombinant p53 gene to treat Head & Neck cancer. It was followed one year later, in 2005, by **Shanghai Sunway Biotech** and their Adenovirus vector also in Head & Neck cancer as well as nasopharyngeal cancer.

Unfortunately, a lot of the ATMP activities in China is still in "grey" unregulated zone of doctors' and hospitals' exemptions. There have for long time been a lot of dubious claims of stem cell therapies curing nearly any disease imaginable, enticing sick foreigners to pay large fees local companies to undergo stem cell treatments at participating hospital. One could say they were conducting "guinea pig" experiments on human's as there were clinical trial data supporting claims made. Some of the first cell-based companies were based on such business model. Frist CFDA and now NMPA have been cracking down and strengthen regulations and enforcements. Still there are a lot of questionable practices ongoing in the academia, such as conducting clinical trials with unapproved ATMP:s developed and produced locally at the hospitals under non-GMP conditions, exposing patients for large risks.

Another example of controversial and unethical "gene therapy" research conducted by the Shenzhen based doctor, He Jankui, that used CRIPSR-Cas9 techniques to alter genes of twin baby girls born at the end of 2018 to make them resistant to HIV. Chinese government was quick to react outlawing the practices and indict the doctor,

There is certainly a need for more stringent regulations and enforcement to remove unethical and potentially harmful practices of testing ATMP on patients in China.

On the positive side there is large R&D investments from the central government coupled with excessive funds from local and provincial governments, as well as available from private sources. However, a lot of it is inexperienced and "dumb" capital, which have limited resilience and are usually rather short term, not understanding the long development cycles in biopharma and ATMPs.

According to Nisa Leung, Qiming Ventures the PE and VC investments in China increased from roughly USD1bn in 2012 to USD11 billion in 2017. However, in 2018 VC fund raising dropped to half of 2017 level. At the end of 2018 it was > USD100bn in state, provincial and local funding for life science available. The HKEX listing offers one additional avenue to raise additional funds for companies that have made progress in their clinical development, but still don't have revenues or at least not profitable. Another more recent possibility for raising money through an IPO in China was started on July 22, 2019 by the Shanghai Tech Board, "STAR Market".

The number of cross border deals and deal sizes are constantly going up and Chinese companies are now willing to pay serious "bio-dollars" for premium assets. Even though you sometime may question if there is any sound economical thinking behind as the prices on the local Chinese market are too low to recoup the investment, but that is for later …

Public opinions

It is difficult to know as any diverging opinions from the official line are tightly controlled.

SME companies ("Bio-Ventures"), Industrial players, domestic Big Pharma and MNCs

NOTE; Names in English and Chinese language of Chinese companies are often very far apart and cannot be reciprocally translated. Furthermore, every Chinese company have a city or a province in its official name.

There are a lot of innovative life science companies being set-up often led by US educated returnees. However, many has unrealistic expectations and nowadays may also get too much money. The challenge is to find companies that have whole teams of competent staff and an ability to retain talent as turn-over is typically very high in China.

Of the about 7,000 pharmaceutical companies in China probably around 90% are dealing with generics and copy-cats at rock bottom prices. However, the early exporting pharma companies from 90ies, when they were solely in API manufacturing moved on to generics, then to innovative small molecules, biosimilars and now into innovative biologics. Hengrui Medicine and Hansoh Pharmaceutical are example of such companies. This is two public companies lead by a husband and wife team, with HQ in Jiangsu province. Now, on paper among they are among the richest couples in China. **Hengrui Medicine** also happens to be the Chinese company with most innovative drugs in the pipeline, whereof a lot are biologics including some ATMPs including CAR-T. This is just an example to illustrate the rapid transformation some companies have gone from API to ATMPs.

In 2017, Hengrui became the first Chinese pharma company to reach RMB200billion in market cap (~USD30bn), which is still rather small to Western peers.

One of the first CAR-T investments coming to public attention was WuXi AppTec's JV with Juno created **JW Biotechnology** in April 2016, but it's faltering and is now said to being dissolved according to industry insiders with WuXi going alone in China offering ATMP CDMO services.

A year later **Fosun Pharma** created a JV with Kite with an initial payment of USD60M + USD35M in development milestones

The most famous are probably **Nanjing Legend Biotech** (www.legendbiotech.com) a subsidiary to **GenScript Biotech** Corp. that signed "bio-dollar" deal (USD350M upfront!) with Jansen of JnJ in 2017. In 2018 the spectacular clinical trials results presented at ASCO Dec 2017 came into question, with best data selectively presented from the least established hospital in Xian as well as under reporting a death occurring in the clinical trial highlighting the risk with CAR-T therapies. The Legend stock price went for a rollercoaster ride in 2018 first surging 440% and then

loosing half its value, but Jansen have stood by Legend and continued the collaboration and excellent response data initial reported was confirmed and reported at ASH2018. In April 2019, EMA granted Jansen and Legend PRIME designation in EU (Priority Medicines).

Other mainland Chinese companies actively involved in CAR-T is **UniCAR Therapy** with at least 5 CAR-T clinical trials working together with Japanese Terumo for production in Shanghai of clinical trial material. UniCAR has treated more than 400 patients and have more than 30 patents related to CAR-T technology.

There is a long list of companies at least interested in this space; **3SBIO** (invested in Sorento and Refuge Biotech, both in US) and **CARsgen Therapeutics**, **Persongen** with Anke Bio as an investor USD3M which is next to "nothing", **Beijing Immunochina Pharma**, **Galaxy Medicine**, **Gracell Biotechnologies**, **Genechem**, **Dasheng Bio**, **Hrain Biotechnology**, **Minghui Bio**, **Boruida Biotech**, and **Innovative Cellular Therapeutics**. Some of these companies even with CAR-T and other ATMPs in clinical trials, but financial limitations, lack of manufacturing expertise, etc could easily stop the activities and wipe them out. Chinese life science sector is extremely dynamic and companies that thrived two years ago may not even exist today.

Cellular Biomedicine Group (CBMG) got a stamp of approval in October 2018 when Novartis announced USD40M investment letting them produce Kymriah CAR-T in China.

Other Chinese companies focused on cell or stem cell derived therapies are **Tianjin AMcellgene**, **Beijing Health-Biotech, Beijing SH Biotechnology, Cell Biomed Group, Qingdao Allcare Biomedical Development**, and **Shanghai IXCELL Bio**.

Pre- and clinical development.

There is usually fierce drug development competition for every known target and molecule. China joining ICH has open the flood gates to using Chinese patients for international registrations. However, high quality CROs with proper and correct documentations meeting global standards are in short supply at the same time prices for clinical trials has gone 10x per patient of more, for the best hospitals and best CROs.

However, there are a large number of treatment naïve patients in China and a willingness to participate in trials in order to get access to new and innovative treatments for free. It is typically 3x – 10x easier to recruit Chinese patients to cancer trials than in the West.

Large clinical trial centres in China typically see more than 20x more patients than the largest centres in EU/JP/US.

There is very strong Chinese governmental support to become the global leader of clinical development and clinical trials. Large domestic Clinical CROs are rapidly

growing even bigger and for instance WuXi's clinical CRO arm has grown to become the second biggest in China and may soon overtake the leader to become the largest clinical CRO. WuXi has built up a lot of experience and have the capabilities to take on any type of clinical trials also ATMPs.

Furthermore, overall China is quickly becoming much better coordinated and to incorporate real world data, risk-based monitoring and new technologies in clinical trials, at least at its leading clinical trials centres.

It's crucial to conduct audits by independent reviewers with western experience and ability to communicate and read mandarin, at least one person in the audit team. Check integrity, documentation, knowledge of and ability to follow SOPs, check-out CAPA. How many corrective and preventive actions has been taken? Are the records too perfect (it often is in China!)? What has been done? Check out USFDA and EMAs inspection / audit records if any!

It's also important to remember that clinical practices are often different in China and to West. Through-put the number patients per hour is one of the most important aspects. Medical doctors do not have same high status as in the west, and pressure on the best hospitals are enormous at the same time as salaries are relatively low, which explains why corruption is still rampant.

Hospitals in China are organized according to a 3-tier system that recognizes a hospital's ability to provide medical care, medical education, and conduct medical research, either as Primary, Secondary or Tertiary institutions

A primary hospital is typically a township hospital that contains less than 100 beds. They are tasked with providing preventive care, minimal health care and rehabilitation services. Secondary hospitals tend to be affiliated with a medium size city, county or district and contain more than 100 beds, but less than 500. They are responsible for providing comprehensive health services, as well as medical education and conducting research on a regional basis. Tertiary hospitals round up the list as comprehensive or general hospitals at the city, provincial or national level with a bed capacity exceeding 500. They are responsible for providing specialist health services, perform a bigger role with regard to medical education and scientific research and they serve as medical hubs providing care to multiple regions.

Further, based on the level of service provision, size, medical technology, medical equipment, and management and medical quality, these 3 grades are further subdivided into 3 subsidiary levels: A, B and C. This results in a total of 9 levels. In addition, one special level - 3AAA is reserved for the most specialized hospitals.

Previously there were a list of just 100+ hospitals approved by then CFDA to perform clinical trials. However, after the massive scale of fraud both from CROs and Hospitals detected in the yearlong review of all submitted generic application to CFDA a few years ago, the system changed completely after China joined ICH in

2017. Now any hospitals could participate in clinical trials as long as certain quality standards are met and certified.

Manufacturing

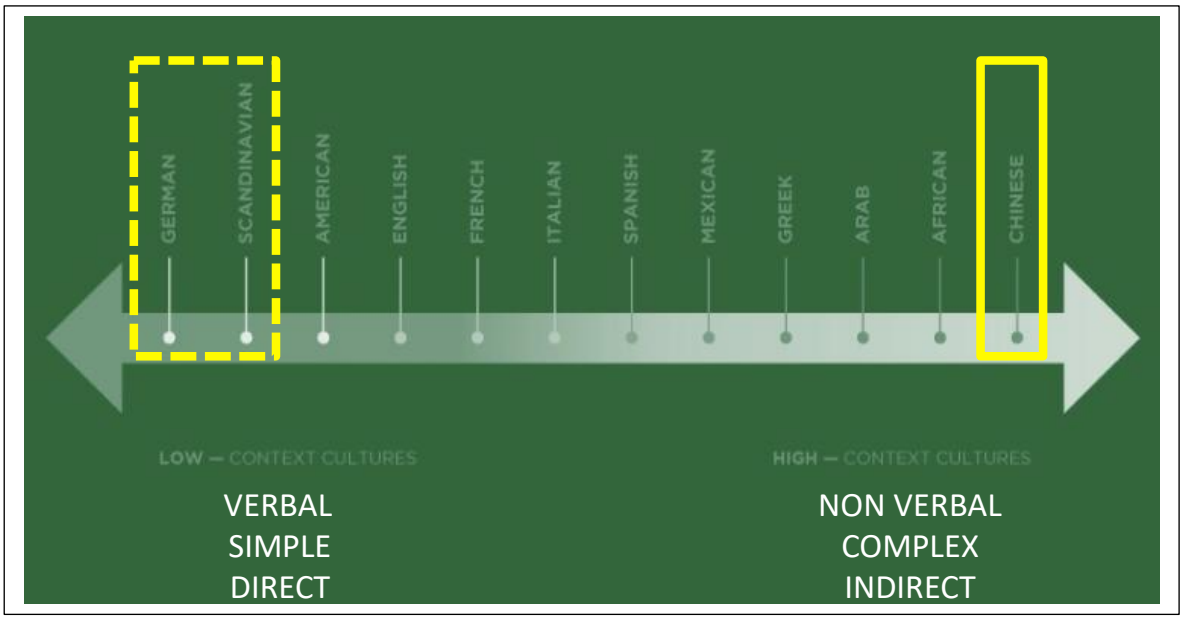
It is just a few years ago that the concept of Market Approval Holder scheme was introduced in China for biologics making it possible to outsource production to a CDMO or a partner company without the originator giving up the market rights. The only product category that is not covered by the MAH-scheme is vaccines, defined as prophylactic vaccines, due to national security concerns. However, there may be some grey area when a cancer vaccine is a therapeutic vaccine which should not be prevented from using the MAH-scheme and when it is just prophylactic.

In general, the biologics manufacturing facilities being built are becoming better and better from a design, lay-out and equipment point of view. However, Quality management system and “quality culture” are still lacking and are far behind the West. Furthermore, there are few complete teams that are able to handle complex ATMPs manufacturing. There are certainly skilled individuals available, but to recruit, maintain and retain such individuals is a challenge let alone to build a complete team.

One should not underestimate the differences in operational scrutiny and the willingness to take risks by Chinese companies.

Manufacturing of API and small molecules holds higher standards, but a lot of data integrity issues and other GMP critical deviations have been found during inspections by European or USFDA personnel, which are well documented and publicly available.

Examles of some CDMOs in ATMPs are GeneScript, the parent company of Nanjing Legend, WuXi Biologics, and CMBG.



2.2. Bus. Dev. Considerations

Chinese business culture is in-direct and with high context, and complex. It's not at all like the Scandinavian direct way of communicating. See the figure above.

A Chinese may interpret you actions totally different from what you think you have done and said. See illustration below of cultural differences affecting communications and understanding between parties. Many (if not most) Chinese companies are run top-down with an emperor on top. Lower and Middle managers do not dare to go outside the scope or take any chances as it may jeopardize their work future. Thus, seek contact and meetings with the real decisions maker(s), usually Chairman (majority owner), which may also be the CEO.

Personal relationships are the most important in business development dealing in China either acquired through net-work contacts or by slowly built-up through your own net-work. To meet face-to-face in person several times, taking time for off-work interactions are crucial to build a long-term relationship and future business success.

As a highly organized Swede, with a clear structure and pre-planning in high regarding a Chinese counterpart will look chaotic and disorganized. When a Scandinavia plan something 1 – 3 months advance, an overseas Chinese returning home may plan it in 1 – 3 weeks in advance and a local Chinese 1 - 3 days in advance, which may actually be the best-case scenario. Don't be surprised of last-minute changes and that people don't show up. Be flexible, avoid too tight schedules allowing sufficient time for changes and additional activities not pre-planned.

The concept of time is different. Time is not linear but cyclical or circular. "It's always a day tomorrow".

In State-owned-Enterprises (SoE) such as large health care conglomerates, Sinopharm or Shanghai Pharma, top managers are vice ministers in the government, public officials with little room to maneuverer and also restricted to travel abroad.

- Build your own network, aim for long term relationships and show that you will be there for the long run.
- Establish your intentions by having a local presence in one way or another.
- "Everything in China is business" in the sense what you do in private and conduct yourself reflect how you carry out business activates. If you show everything from the outset (after a signed CDA – which is just a piece of paper), then you are a poor businessman equal a loss of trust! You share information piece by piece and keep some leverage!
- Be patient, be polite and live by local rules!
- Due diligence is essential – Audit, Inspect and Verify, Audit, Inspect & Verify….
- Build up your market understanding. The Chinese population and prevalence do not equal market size. It is far more complex. Prices are often very low. Don't be

surprised if an innovative treatment is priced 90% - 95% lower in China than in EU & US, at least if it is procured centrally and reimbursed by the Public Health Insurance system either on provincial or national level.

- When a deal has been signed, don't be surprised if renegotiations start immediately.
- Do the deal with a Hong Kong registered company with HK law if possible.
- In mainland China, when the other party is a mainland Chinese company mainland Chinese law prevails, regardless of what the agreement says.
- Remember company names are totally different in English and Chinese. Make sure you do the deal with the right company there are always sister companies, daughter companies and nephew companies
- Make sure to get some payment upfront it might be the only thing you get …

Chinese companies are often more willing to take equity stake in a western SME, but this could be a blessing in disguise. The risk of IP leakage increases and a minority stake from a Chinese investor may prevent access to some cautious western investors, as well as degrade the value of the company. Very carefully conducted due diligence and in-depth risk assessments are recommended. There are certainly very competent, legally and ethically sound Chinese corporations with international business operations (and foreign legal entities) that would be attractive partners, also from an investment and equity point of view. Others may be better to do a trade sale with.

The interest in Sweden and Swedish life science companies is high and increasing especially with the more hostile environment in US with its updated legislation "The Committee on Foreign Investment in the United States" (CIFUS) that reviews various tech investment from a national security point of view, very much with in Chinese investments in mind. In 2018 President Donald Trump signed the "Foreign Investment Risk Review Modernization Act" (FIRRMA) which gave CIFUS new powers.

<u>IPR, Chinese laws & Arbitration procedures;</u>

The patent law has been further improved, but the devil is in the details and in the implementation. There is a drug patent term compensation system in development. Innovator's patent protection has been further strengthening.

Furthermore, China is now accepting the UNCITRAL rules from 1959 for international arbitration, even though local Chinese arbitration authorities have their own rules. It is always a safe bet to have agreements with arbitration in Hong Kong as it has been recognised in mainland China for a long time. The acceptance of international arbitration rules is partly to help protect Chinese companies going abroad.

2.3. Regulatory Affairs & Custom control

China National Medical Products Agency – NMPA, previously known under other four letters acronyms such as CNDA (Chinas National Drug Agency), CFDA (China Food & Drug Agency, when food was handles by the same agency prior to the 2017 reorganisations), SFDA and SDA (when the agency was first established).

Several regulatory reforms have been enacted during the last two years and others are ongoing or coming in the near future. The most important by far is China joining ICH in 2017. More about that little bit further below. First the official Policy Objectives from the Chinese government's perspective:

1. Inspiring structural shift of industrial and technological innovation of the pharmaceutical industry (a part of the controversial "Made in China 2025" policy.
2. Improving domestic competitiveness within pharmaceutical R&D.
3. Improve access to new innovative therapies (a population demand!) by speeding up progression of clinical trials and marketing approval process.
4. Encouraging life science innovation in the pharmaceutical industry.

I would also like to add:

- ✪ Create global pharmaceutical champions, increasing Chinese export of medicinal products to advanced economies.
- ✪ Create innovative block buster drugs developed and manufactured by Chinese companies.
- ✪ Reduce the number of domestic pharmaceutical companies and move on from copying generic drugs to true innovation and novel therapies.

China joining ICH in the summer of 2017 greatly removed a lot of hurdles as regulatory reform has accelerating and new rules have been streamlined with ICH. By implementing such internationally regulations in China, foreign clinical data are now accepted in submissions for approvals. There are some caveats such as showing any population differences. Previously a drug candidate had to be in clinical Phase 2 or Phase 2I studies or having received market approval abroad or in the "home'-market before an international multi-centre trial (IMCT) could be started in China. That hurdle is now removed!

Similarly, Chinese clinical data (of correct quality and documentation that is!) could be used in EU and US. And the Chinese government would like China to become the clinical trial centre of the world as they now understand how important possession of clinical data is from a "big data" point of view. There are tales about Chinese companies that went straight into Phase 2 in US based on Chinese Phase 1 data.

In 2018, NMPA formerly announced that there will now be a tacit approval of a Clinical Trial Application (CTA) after just 60 days, unless the authority has issued another

decision within the given time period. Previous it often took 12-18 months for domestic companies and more than 2 years for foreign companies to get a CTA approved.

APIs and formulation, which previously were approved separately, can now be linked and approved together as well as with excipients and packaging.

Fast track and priority review of drugs addressing high unmet medical needs, such as in cancer are in place as well as possible conditional approval for ATMPs after Phase 2 when there are no other treatments available. NMPA can now also give conditional approval based on surrogate endpoints for drugs addressing medical unmet needs, such as cancer therapies.

In 2017 NMPA for the first time introduced the concept of Orphan Drug Designation (ODD) in China. However, it is not based on a certain percentage limit of prevalence or incidence in China, instead NMPA has compiled a list of diseases and conditions that qualify for ODD. The real challenge for ODD in China is the lack of premium pricing and generally very low prices even on innovative medicines at least if the therapy is to be covered by the National Health Insurance. Now, China's NHI has promised higher payments, but what that means in reality remains to be seen.

Another important change is the full implementation of the Market Authorisation Holder (MAH) program for biologics, which have not only increased protection for the innovator company, but also made it possible to use CDMOs for manufacturing of biologicals drugs including ATMPs.

NMPA has also been establishing a professional drug inspector system, increasing the number of reviewers and inspectors. Previously CFDA and CDE, the Centre for Drug Evaluation, had only 125 reviewers. In 2017 it was around 300. Larger degree of so called "internal out-sourcing" of reviewing among the different CFDA departments. For instance, National Institutes for Food and Drug Control (NIFDC) now do some reviewing that previously was done by CDE.NMPA's and CDE's staff continues to grow and is said to be above 600, but the new people hired need to be full trained and need to be retained. NMPA must avoid losing talent to local industry, at least now during the ramp up.

During the last two years several documents have been published by NMPA pertaining to ATMP development such as; "Technical Guidelines for the research and Evaluation of cell Therapy products (Trials)" and "Opinions on encouraging drug innovations and priority review and approval from the General Administration". The latter covers cellular therapies and CAR-T and what is required to be able to qualify for priority review, etc.

Preparations & Submissions to NMPA;

Below some suggestions from experienced industry insiders that have made several submissions in China to start clinical trials and to get market approval to start commercialization, both under the old and now with the new rules and regulations.

- Translation into simplified Chinese only by very experienced regulatory affairs personnel with true bilingual ability. Chinese language frequent use of idiomatic expressions and erroneous translation are common especially by Chinese educated abroad returning in China after many years in the West. Remember to build in sufficient time for translations and QC of the translation in the project timeline.
- Submit applications written both in English and Chinese using a disclaimer that "in case of doubt, the English version shall prevail". It will effectively double the size of a submission but remove any concerns from HQ regarding correct wordings in the submissions. If the NMPA asks, then submit additional documents as requested.
- Make sure all data from EU and US are included and well explained.
- Typically, there are requirements by CDE of additional tox. data compared to EMA and USFDA.
- Formal consultations with NMPA and CDE is possible, but only in Chinese!
- If there are any doubts make sure to carefully check that there an established testing method at CIQ if you need to import the therapy under development to China.
- Carefully assign a competent and experienced vendor/partner that will import any clinical trial material in China unless it's locally produced.

Note, the regulatory landscape in China is very dynamics with new guidelines, laws and regulations being implemented constantly. Thus, it is difficult to be 100% up the date all the time and thus some of the most recent implementations may not be included in this report.

IMPORTANT! Blood and tissue samples are not allowed to be exported and shipped abroad, not even to Hong Kong and Macau! Import is also strictly limited.

Any import of biological material, reagents etc., needs to be controlled and tested by China Inspection & Quarantine (CIQ) at China custom control. Each mainland Chinese province (22), autonomous region (5) and municipality (4; Beijing, Chongqing, Shanghai, and Tianjin) has its own CIQ.

It is not uncommon that custom clearance takes too long time and biological specimen, reagents and products are totally spoiled during the waiting time. Therefore, it is essential to engage with a proper distributor or logistics import/export

company, preferentially one with Green Channel priority through CIQ and Chinese customs. There are only a few such companies for biologic specimen in China.

2.4. Price & Reimbursement

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

However, what hasn't change is the notoriously low prices especially if a therapy is reimbursed on a national level. Furthermore, various procure schemes like the new 4 + 7 (the 4 municipalities + key provinces) procurement procedure for essential drugs are further reducing prices. Very recently the National Healthcare Security Administration (NHSA) revealed that 4 +7 process will now be enacted nationwide, in a stepwise process starting with a pilot program with a full implementation expected during H1 2020. The new scheme will include a few changes, allowing three winning bids for each therapy. Thus, regardless in order to make money a low COGS is necessary including a cost-efficient marketing & sales + distribution channels.

Of course, new innovative therapies could be launched at any price, which wealthy and privileged patients with private insurances may be able to cope with. The market size would just be much smaller than otherwise anticipated.

Many western pharma executives far often greatly overestimate the market size and value in mainland China by equalling the Chinese population, prevalence and incidence rates with an assumed market size. In reality inequalities across China, large differences between large cities and rural communities in terms of therapeutic practises, options and hospital care plays large roles in determining a more appropriate market size. Additionally, the inefficiency to reach out to patients making them aware of their disease as well as treatments available is another large hurdle. Even in a common disease like diabetes, penetration rates are probably still today less than 50%. In Q4 2014 it was just 15%! There are more than 100million people with diabetes in China!

Another "reform" to keep prices down was introduced a few years ago called "two invoice system" meaning that only two invoices would be allowed, from the producer and the distributor. There cannot be several layers of sub-distributors and dealers between the producers and the pharmacy/hospital. This in order to both cut corrupt practises and bribery as well as keep prices down as hospitals have been forced to abandon any mark-up of therapy prices.

However, country side hospitals have been hurt as many distributors doesn't cover all of China and reply on local distributors and dealers to each everywhere.

At the same time the Chinese government have offered more incentives for drug and device innovation, including more flexible reimbursement coverage and potential patent extension.

China has sped up reimbursement decision and listing as well as including innovative biologics and small molecules. Furthermore, China has invited foreign companies to submit innovative therapeutics for local approval through a high priority, Fast Track approval process, to mitigate serious gaps in accessibility of new medicines and take care of unmet medical needs.

Recently, several innovative biologics have been approved in China by NMPA.

More recent inclusions during 2017 and 2018 have dramatically increased the reimbursed prices, to on average USD1,996 in 2017 and USD 2,141 in 2018 per month of treatment, using exchange rate of 6,90 RMB/USD. Still prices are far lower than EU and US.

Local and foreign companies launching new treatments on Chinese market without being reimbursed often offer patient access programs. One example of a recently high-priced PD-1 inhibitor from Hengrui, the most expensive of all PD-1s approved in China are now covered by a patient access program greatly cutting price further. The scheme can be summarized as “Buy two, get two free; buy another four, get one year free”. This means enable eligible patients who pay for 2 medication cycles will receive 2 more free of charge, and then once purchasing 4 more medication cycles will receive a one-year course of treatment (capped at 18 shots) also free of charge. These types of drugs will not be available everywhere, but just at leading hospitals in top Tier cities and municipalities. Thus, a China wide marketing and sales strategy may not work depending on a drugs particular reimbursement status and what price is used.

It’s quite telling that China got the world first gene therapy approved more than 10 years ago. There are several mAb:s and recombinant insulin on the market and recently the first CAR-T was approved , but there is no biologic drug among the top 20 best selling drugs in China! The best-selling drug in 2017 would not even be considered a drug in the west, it was NaCl injectable, sold for USD2.3 billion!

<u>Considerations for commercialization of therapies in China:</u>

- > 20.000 hospitals in China
- No premium pricing, prices are typically 50% - 90% lower than in the West for innovative drugs!
- Central procurement of essential drugs with several provinces coming together to lower prices even more under the national reimbursement level.
- Re-imbursement for drugs 20% - 90% if on the B-list, provincial and municipality level.
- Find a partner having the necessary experience & competence to handle:

⇒ Regulatory Affairs, and submissions to NMPA

⇒ Marketing & Sales

⇒ Good distribution channels targeting selected cities (Tier 1 and 2) / provinces to high quality Tertiary (perhaps Secondary) hospitals

⇒ Then carefully monitor Regulatory Affairs, CFDA submission documents etc.

3. Japan

A strong sentiment of being unique – Japan is an island (or island) just like UK!

Japan is the third largest market for prescription medicine and advanced health care, but CAGR is low, around 2%, as price pressure is downwards, but the ageing population contributes.

3.1. Local ATMP environment

NOTE; in a local English vocabulary ATMP is known as Regenerative Medicine.

There are several academic and industry organisations that are involved in policy and regulatory development, acting as expert bodies when revisions are proposed to Pharmaceutical & Medical Device Agency (PMDA) and Ministry of Health, Labor and Welfare (MHLW) regulations, as well as price and reimbursement issues.

There are several important organisation to consider for net-working and lobbying depending on the therapeutic area a company is involved in, such as Japan Society for Haematology (JSH), Japan Society fort Regenerative Medicine (JSRM), Japan Society for Hematopoietic Cell Transplantation (JSHCT), Japan Society for Paediatric Haematology (JSPHO), Japan Red Cross (JCR), Forum for Innovative Regenerative Medicine (FIRM), Japan Bioindustry Association (JBA) and Japan Pharma Manufacturing Association (JPMA).

Every year in the middle of October, Japan BIO is held in Yokohama. It's partnering conference, but there are also parallel sessions with presentations and panel discussions on various topics. ATMPs have always a high priority.

Market sentiments

ATMP stakeholders have been excited by regulatory changes enacted in 2014. It seemed to have paid off as the legislation has helped to ramp-up domestic development of ATMPs. Previously it was mainly driven by academia and a few new players, start-up companies, so called "Bio-Ventures" (domestic SME Biotech). Then some large Japanese companies from other industries entering the life science area such as Fuji Film and Hitachi Chemicals and finally Japan's pharma companies are coming onboard.

Most of the traditional medium size and large Japanese pharma companies have mainly remained on the side-lines taking their usual risk averse positions. However, during the 2 -3 years there have been a quite dramatic shift with several pharma

companies coming into play by licensing deals or establishment of co-development partnerships with local academic institutions such as Takeda with Kyoto University. It's an example of the usual herd mentality in the industry.

There is a clear lack of VC-capital in Japan. Funding is predominantly from the government and from cash rich R&D focused companies, but with the risk awareness and conservatism in the industry new ideas have often difficulties getting substantial funding.

With respect to organ transplantation, which was not included in the 2014-legislation, and as there are too few organ donors for cultural/religious reasons, thus regenerative medicine has created hope that cell therapies / artificial auxiliary organs could be used in future. Changes to Public Health insurance will be necessary when ATMPs are widely launched, such as payment models and how much co-payments should be required otherwise the public health care system may not be able to cope with the increased costs.

There are a number of ATMPs approved in Japan some examples are listed below:

- From **J-TEC**:
  - JACE®, autologous cultured epidermis approved to treat serious burns in October 2007 and covered by the National Health insurance in January 2009.
  - JACC®, autologous cultured cartilage approved in July 2012 and covered by the NHI in April 2013.
- TEMCELL® HS Injection MSC-derived allogenic therapy for acute GVHD by **Japan Chemical Research** (**JCR**) approved in at the end of 2015 as an ODD.
- Heart Sheet, from **Terumo BCT**, an autologous skeletal myoblast preparation for treatment of patients with serious heart failure based on CellSeed's technology from Prof Okano at Advanced Biomedical Engineering & Science, Tokyo Women's Medical University http://www.twmu.ac.jp/ABMES/en/aboutus
- HGF gene therapy drug for critical limb ischemia from **AnGes** Inc and marketed by Mitsubishi Tanabe got conditional and time limited approval in February 2019, for 5 years. It was the first gene therapy product to be approved in Japan
- Kymriah, from **Novartis** was approved in Japan at the very last day of the FY2018, March 31, 2019.
- Stemirac, an MSC-based therapy from **Nipro** approved in December 2018 for the treatment of spinal cord injury.

Public opinions

Positive impact and national proudness created by Prof Shinya Yamanaka's 2012 Noble Prize in physiology for his work induced pluripotent stem-cells (IPS) at Kyoto University.

SME companies ("Bio-Ventures"), Industrial players, and domestic Big Pharma

Below some examples of Japanese companies involved in ATMPs, from Bio-Ventures to global MNCs.

AnGes Inc, www.anges.co.jp a public listed biotech company established in December 1999 under the name of MedGene Co Ltd in Osaka and changed name in July 2017. Now it has roughly 40 employees. AnGes has several ATMPs in clinical development both of in-house and in-licensed projects. Collaboration with Japanese pharma companies Mitsubishi-Tanabe and Shionogi. AnGes has subsidiaries in US and UK.

CellSeed, www.cellseed.com, a public tissue engineering company (JASDAQ) established 2001 and built upon the cell sheet technology developed by Prof Okano and his team at the Tokyo Women's Medical University. By using temperature responsive polymers, it is not necessary to use enzymes to remove expanded cells grown on surfaces. The technology has been used by other companies and various academic groups in japan and overseas to develop cell-based therapies such as Terumo BCT's Heart Sheet. The company has less than 50 employees with a revenue of roughly USD 9.5M in FY2018.

CellSeed has a Swedish subsidiary.

Japan Tissue Engineering Co Ltd (J-TEC), www.jpte.co.jp a public listed company (JASDAQ), celebrated 20 years anniversary this year as the company was founded in 1999. The biggest shareholder is **Fuji Film** (50.1%) and as such a consolidated subsidiary since October 2014. The company has roughly 185 employees.

Apart from developing their own cell-based therapies, J-TEC also offers CDMO and R&D support. The company is unusual as it located in a small town, Gamagori in the Aichi prefecture some 60km from Nagoya along the coast of Japan.

Junten Bio, www.juntenbio.co.jp is a regenerative medicine drug development Bio-Venture established in 2018, which **Fuji Film** decided to invest in June 2019. J-TEC is supplying regulatory affairs services and Medinet got a contract to manufacture their drug candidate.

Medinet Co www.medinet-inc.co.jp a public listed company established in 1995 offering CDMO services. It has nearly 100 employees and in FY2018 the revenues were roughly USD9M.

Nipro Corp., www.nipro.co.jp is a relatively old public listed Japanese medical company established 1954 with more than 19,000 employees in the corporate group. It has both medical device and pharmaceutical business, as well as offering CMO services. It was the first Japanese company to get a tissue engineered medical product created from stem cells approved.

The company has an MSC-derived treatment for spinal cord injuries approved in Dec 2018. It was co-developed by its medical device divisions and Sapporo Medical University.

Terumo BCT, https://www.terumobct.com/ established in 1964 belongs to the Terumo Group of companies founded in 1921 and listed on TSE. Terumo BCT has blood collection centers worldwide, and also offers CRO and CDMO services for blood and cell-based therapies having more than 40 years' experience in the field of blood and cell separations for autologous cell therapies. The company has nearly 7,000 employees globally with manufacturing facilities in Asia, Europe and North America. HQ is now located in the US.

Furthermore, the company offers automatic CAR-T cell manufacturing technologies. For instance, Terumo BCT is working together with UniCAR Therapy in China and recently created a Shanghai based China Centre of Excellence for UniCAR's manufacturing of CAR-T therapies.

Local major pharma companies such as **Astellas**, **Daiichi-Sankyo**, **Dainippon Sumitomo**, **ONO**, **Shionogi** and **Takeda**. The latter, especially after the acquisition of Shire, have all their own ATMP efforts collaborating with both local and foreign academic institutions and companies. Takeda recently signed a collaboration agreement with the Centre for iPS Research & Application (CiRA) at Kyoto University using iPS for CAR-T called iCART to create an off the shelf CAR-T, an allogenic therapy.

Astellas is the other top Japan pharma company with a lot of R&D activities in the ATMP field, as well as the expertise and infrastructure for GMP cell manufacturing. The company has its own Institute for Regenerative Medicine and is investing heavily in the field. The latest deal came in the middle of July 2019 when the company paid USD80M upfront for a regenerative medicine candidate from US-based Frequency Therapeutics with up to USD545M in milestones for global rights outside of US.

Daiichi-Sankyo entered into an agreement with Kite in January 2017 paying USD50M upfront. The companies agreed to work closely together for the development, manufacturing and commercialisation of Kite's CAR-T therapies in Japan.

Pre- and clinical development.

Until five years ago ATMP development was predominantly driven by academia, with only a few Japanese pharma companies involved. That has changed dramatically during the last years with essentially all major Japanese pharma companies involved.

There has long been an opinion in the West that running clinical trials in Japan is expensive and a complex operation, but it all depends on what partner you have, the CROs you are using their experiences and bilingual capabilities. The fact to matter is that Japan has on average had 0% inflation the last 25 years, but the exchange rates

has changed. Costs are high but could be kept down by utilising experienced project management as well as to include Japan in global Phase 2I studies and use patients from other cheaper Asian countries for regional multi-centre studies.

There are relatively few foreign SME companies conduct clinical trials in Japan, due to a lack of knowledge of what is required, but again selecting the right advisors and CRO it should go smoothly as long as enough resources has been allocated and in return the company would get high quality in GCP documentation and data collection.

With the right consultants for regulatory affairs / CRO / hospitals, it could be very quick as Japan is one of the fastest countries in which to begin clinical trials. There is a need to motivate doctors and give adequate support, but ATMPs are in "fashion" and followed by great interest.

It takes typically 4 – 7 months from submission to first patient in.

Case; US-company conducting Phase 1 bridging study in Japan with an ATMP in a rare cancer (ODD). The time from submission to PMDA, recruiting 10 patients treating them, follow up and reporting ten (10) months! This allowed the US company to include Japan in the global Phase 3 study.

There is a clear advantage from a business development point of view of creating an interest with local KOLs and potential licensees by carrying out your own clinical trials. The uncertainties for the Japanese BD manager is reduced and you could negotiate in parallel.

Manufacturing

Local manufacturing facilities in Japan are being developed using a high degree of automation for aseptic cell processing using isolator technology and by utilising knowledge from robotic work stations used in the semi-conductor industries cross fertilising into cell and gene therapy pilot plant manufacturing units, such as Shibuya Corp. https://www.shibuya.co.jp/english/sby/.

ATMPs are typically manufactured locally at hospital sites within the hospital exemption provisions, but specific CDMOs have also emerged, like J-TEC, Medinet and Foundation for Biomedical Research and Innovation (FBRI) in Kobe. The latter was contracted by Oxford Biomedica, to manufacture the lentiviral vectors for Novartis' Kymriah.

Traditional Japanese industrial companies have moved into life sciences and CDMO business including ATMP manufacturing such as, Fuji Film Diosynth Biotechnologies and Hitachi Chemicals Advanced Therapeutic (http://hitachi-chem-ats.com/). Japanese CMOs with at least viral vector manufacturing capabilities and pharma companies offering its services to others includes AGS Biologics, and Takara Bio.

3.2. Business Development Considerations

Decision making in Japan is very similar to Sweden. It's mainly built on consensus, where a group of senior managers come to a coherent view and unanimous decision. In some larger organizations the Chairman and CEO may just be figure heads, while the real decisionmakers are in the next level below. However, there is typically a strong trust to their leaders or authority, Customer / Sales, Senior / Junior, Doctor / Patient.

Japanese businesses are risk averse or rather avoiding uncertainty. In order to cope with this anxiety from a Japanese manager, minimise the uncertainties and the chances of reaching an agreement increases dramatically.

Japanese are low key, follows the group and don't stick their necks out!

Relationships are important, and so is university and its ranking, company and bureaucracy. Traditionally the best graduates from the top universities always went to the bureaucracy, with major companies as second choice, while foreign companies came a distant third. Therefore, when serious problems occur, personal net-works among friend from top universities prevails and a foreign company with local presence in Japan may have difficulties in getting issues resolved that requires involvement of ministries or other bureaucratic bodies.

Businesses is still very male dominated and English abilities are often poor. The language barrier easily creates misunderstandings and really highlights the importance of face-to-face meetings, bringing in bilingual advisors are recommended.

Another, obstacles experienced with some Japanese companies are their European offices which often have young Japanese staff good at English, but without any hierarchical power. They are just following instructions without the possibility (not allowed) to think outside the box. Thus, there is not much flexibility at all. Therefore, it is often much better to establish contacts directly with the HQ in Japan.

Typically license deals in Japan are better paid than similar deals in China and Korea. Larger upfront are often possible, compared to more back-ended structures in China and Korea, even though Chinese deals are quickly catching up with EU/US-practises.

During the last couple of years more flexibility have been seen and some creative deals have been signed also in Japan, such as option agreement with in-licensing after certain clinical and/or regulatory milestones.

There is a common myth that everything is so complicated and difficult for foreign companies in Japan and that It would be better to have a MNC or a Japanese partner do everything for you. However, by securing your own resources and have good advisors it is possible to develop a medical product using CROs, have a third party as MAH and at the same time maintain control with none or very limited local presence.

Possibilities:

- Out-licensing in Japan as a first step in Asia, better paid, better protection, than most other Asian markets.
- Large demand for new innovative treatments, especially within regenerative medicine and ATMPs.
- Plan ahead and initiate local development and approval on your own to create an interest, show you are sincere and willing to spend, and also create a high value for your out-licensing / distribution deal.

Japanese investors rarely invest abroad, but larger Japanese companies do.

3.3. Regulatory Affairs & Custom control

Japan is one of signatories to the ICH and the Ministry of Health Labour and Welfare (MHWL) encourages companies to carry out Multi-Regional Clinical Trials (MRCT). This would reduce the number of patients needed in Japan, approval could come faster and risk of developing a different treatment procedure in Japan would be reduced.

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

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

I. "R&D Strategy" including Quality and non-clinical Safety prior to or during the pre-clinical development work.
II. "R&D Strategy Pre-Phase 1" before the clinical trials starts in Japan.

it is necessary to use bilingual regulatory affairs consultants (a scare resource) in order to prepare required documentation in Japanese, answer email questions from PMDA (translate for Japanese to English, get the answer from the western company, translate back to Japanese within one working week!), as well as carry out the actual consultations face-to-face. A Western company having carried out PMDA consultations have reduced the risk for a Japanese potential part and would be favourable seen in business development activities.

It would be necessary at the very least before the starting in the participation in a global Phase 3 study. The preparation and conduct of a PMDA consultation take about half a year. To save time, a Phase 1 study Clinical Trial Notification (CTN) could be submitted without a prior consultation. Then, during the 30-day review period, the company will get confirmation whether the Phase 1 study design is

acceptable to the PMDA; the main point being the number of doses required to be studied.

In Japan it's possible to get Orphan Drug Designation (ODD) for therapies targeting disease with less than 5t0,000 patients giving the company 10 years exclusivity period.

The Japanese version of "priority review" and "accelerated approval" scheme through what in Japan is called "Sakigake". This would allow for premium pricing later on.

The "Pharmaceutical Affairs Law" was revised and changed name to "The Pharmaceutical, Medical Device and Other Therapeutic Products Act" (PMDA) came into effect in November 2014 has enabled development of ATMPs with a possibility to come to the market more swiftly if they address high unmet medical needs.

Furthermore, "The Act on the Safety of Regenerative Medicine" (RM Safety Act), must also be considered when carrying out R&D work and clinical trials with ATMPs. The rules and evaluation periods are different depending on risk classification with embryonic stem cells, iPS, gene therapy and allogenic therapies as well as xenografts having the highest risk classification, Class I, which must undergo review by a Health Science Council.

Any cell processing facility outside and within hospitals must undergo review according to the RM safety Act. There are several sites overseas accredited such as in South Korea and Taiwan.

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

In 2017, the ICH issued a new guideline E17 that covers the general principle on planning/designing MRCTs. Japan was a driving force behind this guideline.

According to the MHLW 2007 notification on global clinical trials, if companies conduct a Phase 2 or Phase 3 dose-response or confirmatory MRCT, about 20% of the total should come from Japan.

The E17 guidelines embraces the concept of "pooled populations," where patients with similar genetic polymorphisms are regarded as single populations regardless of their nationality or region as long as external factors such as the healthcare environment are similar. That means if a study is run in East Asian population, or people living in East Asian countries, i.e. Japan, China, and South Korea, this can be treated as a single population. However, if a trial enrolling 300 patients includes 60 East Asians, the PMDA would expect at least about 20, or one-third of the total, to be

Japanese. Again, companies should negotiate with regulators regarding specific trial designs.[1]

There are no data or marketing exclusivity provisions for pharmaceutical products in Japan. However, the effect of post market pharmacovigilance provisions is to ostensibly act as a data exclusivity provision and prevent any generic from coming onto the market during the Post Marketing Surveillance period.

Post Market Surveillance is a process whereby the PMDA re-examines the safety and efficacy of new and previously approved pharmaceuticals later approved for new indications.

For compounds with Orphan Drug Designation (ODD) or SAKIGAKE (similar to US Breakthrough Therapy designation) the re-examination period is 10 years. The ODD approval is conditional upon having less then 50,000 patients who could use the drug, or less than 180,000 patients if the disease is an intractable disease or “nanbyou”. A list of all designated “nanbyou” exists on the Japan Intractable Diseases Information Centre.

Japan introduced the “SAKIGAKE” designation scheme on a pilot basis in 2015, aiming to accelerate the time to market for innovative drug candidates by giving them a series of privileges in both the pre-application and review process.

To be eligible, candidate drugs need to clear four criteria:

1) being novel
2) targeting serious diseases
3) having prominent efficacy
4) being developed and planned for approval in Japan ahead of the rest of the world, or at least simultaneously with other major markets.

To shorten time to approval as well as to facilitate R&D, Sakigake-designated drugs will be entitled to:

1) prioritized consultation
2) extensive pre-application consultation
3) priority review
4) extensive handholding from review partner
5) possible extension of re-examination period (data protection period) up to 10 years

With the PMDA’s pre-application consultation services intended to speed up approval review, the total review time (from application filing to approval) for designated products is expected to be six months compared with the typical 12 months. Once

[1] *ICH Clinical Trial Guidelines Allow Flexibility on Number of Japanese Subjects Needed: PMDA Official;*
Pharma Japan, 2016-07-26

approved, Sakigake-designated products will be eligible for a premium on their reimbursement prices, called the Sakigake premium.

PMDA is really promoting what they call “Regulatory Science” developing methods and criteria for responding to advances in science. Furthermore, PMDA has an informative website in English. www.pmda.go.jp/english .

Blood and tissue samples from Japanese patients could be sent abroad for analysis, testing and expansion. Any cell processing in foreign country must undergo MHLW audit and inspections prior to use in any clinical trials in Japan. Logistically it would be better to do everything in Japan with a local partner or outsource to a CRO and a CDMO.

3.4. Price & Reimbursement

Prices for therapies in Japan are set with references to similar existing products on the Japanese market. If it is a novel therapy, a First-in-Class compound, prices in the three leading EU-markets (France, Germany and UK) are used as reference. US is never used as prices are deemed to be too high.

Some novel biologics oncology therapies have initially received higher prices in Japan compared to when the same compound was approved in US later. For instance, this was the case with ONO’s innovative PD-1 inhibitor, Nivolumab, called Opdivo® by BMS, the first approved PD-1 anywhere in the world. Thus, novel therapies could achieve high initial pricing.

Novartis’ Kymriah, the CAR-T (Cell & Gene therapy) was approved in Japan earlier this year in March and was priced at USD305,000, considerably lower compared to USD475,000 in the US.

When TEMCELL® from JCR was approved in Japan and priced by NHI in 2016 each bag of 72 million cells cost roughly USD7,700. Based on the recommended dosage per adult patient the treatment costs reimbursed would be between USD123,000 – USD185,000.

It’s important to note that Japan does not use pharmaco-economics calculations to set prices for treatments. Furthermore, prices are typically reduced every two years. Thus, it is important to enter the market with a high price.

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

Recently, in June 2019 the Drug Pricing Organization (DPO) proposed lower reimbursement coverage for ATMPs. This has created an uproar in the Japanese

ATMP industry. The ATMP-industry support organisation and an important stakeholder and influencer FIRM strongly opposed such measures during a hearing at the end of July with the Central Social Insurance Medical Council known as Chuikyo in Japanese. FRIM highlighted the different nature of many ATMPs which are given just once in a life time in a curative treatment compared to other higher priced chronic treatments. It was agreed that ATMPs cannot be priced according to the traditional cost-based method. Several proposals were raised and discussions for the FY2020 starting April 1, 2020 is under way how to price ATMPs without causing supply disruptions and encourage innovation and development for treatments for Orphan and ultra-orphan diseases.

Considerations for commercialization in Japan:

- Universal insurance system encouraging innovative drugs and therapies.
- Common drug approval lag gives latecomers opportunities:
    - Become 1st – 3rd instead of 4th – 5th on the Japanese market.
    - By planning and acting swiftly, launching in parallel with EU and US.
- Review period for newly approved ATMPs (RM) is maximum 7 years.
- The normal review period for newly approved Orphan Drugs; 10 years.
- Decide how to handle Market Authorisation Holder (MAH)
    - Set up local subsidiary (MAH)
    - Third-party (“Designated”, D-MAH)
    - Distributor / Licensee (MAH)
- There are few distributors (4 large ones) offering MAH to foreign companies

4. South Korea

A small country mentality being squeezed between giant China and Japan, but it is quickly developing and in many cases on the brink of or already surpassing Japan in the certain life science areas.

4.1. Local ATMP environment

Market sentiments

ATMPs have high profile with a lot of interest from start-up companies, while the larger domestic Korean pharma companies have been more cautious and reluctant to enter the field. It is little bit similar situation to Japan 5 years ago. However, the reason for the reluctancy in Korea is a series of scandals creating additional scrutiny from MFDS making it harder to get new ATMP therapies approved. At the same time Korea seems to have one of largest if not largest number of approved ATMPs on the market. See list of examples further below.

First some general characteristics of the South Korean medicinal products market (prescription medicine and medical devices):

- Considerable smaller market than China and Japan, but still No 13 globally with roughly 1% of global sales of medicines, which is on par with Australia, India and Russia.
- The last 5 – 10 year a dramatic shift from generics to innovative drugs with an increase in R&D expenditures. Previously just a few percent to above 15% of sales for the companies investing most in R&D.
- Increased interest to license-in and to acquire technologies from Europe. Traditionally South Korean companies have collaborated more with US, especially as Korean scientists have been educated in US.
- The South Korean medicinal products market is fragmented market with many small and medium players.
- Some local companies are active also in China and Southeast Asia, which could be beneficial considering possibilities of a regional deal.

There are several ATMPs approved on the Korean market, whereof some are geared towards beauty and anti-ageing such as Tego Science products. Below are some cell-based immune therapies:

- ImmuneCell-LC, the cell-based immune therapy from **GC Cell**, that got conditional approval already in 2007 for liver cancer and later expanded to other cancers as well. More recently, in 2018 it was granted ODD status in US for pancreatic cancer.
- CreaVax RCC® from **JW CreaGene**, a cell-based immune-therapy dendritic cell therapeutic vaccine for metastatic renal cell carcinoma, approved in 2007

Other cell-therapy products, including ones derived from stem cells:

- Adipocell®, from **Anterogen** autologous adipose derived MSC therapy s.c. fat tissue repair
- Caristem® from **Medipost** for Osteoarthritis, an umbilical cord blood derived MSC allogenic therapy approved in January 2012.
- HeartiCellgram®-AMI, from **FCB Pharmicell**, an autologous bone-marrow derived MSC therapy for Acute Myocardial Infarction (AMI) approved in July 2011
- Chondrom™ autologous chondrocytes from **Regenerative Medical System** (**RMS**) / **Sewon Cellontech** approved in 2001.
- Cupistem® Injection from **Anterogen**, an autologous adipose derived MSC therapy for Crohn's disease approved in July 2012.

- CureSkin, from **S-BioMedics,** a Belgian company, is an autologous dermal fibroblast cell-based therapy approved in 2010 for the treatment of depressed acne scars.
- Holoderm® from **Tego Sciences**, autologous keratinocytes for wound healing and regeneration of the dermis and development of new skin, indicated for treatment of various skin disorders and burns approved in 2002.
- Hyalograft-3D™, from **Cha BIO & Diostech,** is an autologous skin fibroblast cell therapy on 3D scaffold formed of hyaluronic acid derivatives for the treatment of diabetes foot ulcers, which was conditionally approved in 2007.
- Kaloderm®, from **Tego Sciences** is an allogenic cell therapy for deep 2nd degree burns, and diabetic foot ulcers approved in 2005 and 2010 respectively.
- KeraHeal™ (autologous) and KeraHeal™-Allo (allogenic) keratinocyte therapy from **BioSolutions**, for 2nd degree burns approved in 20016 and 2015 respectively.
- Neuronata-R® injection, from **Corestem**, an autologous MSC therapy for treatment of "Near Amyotrophic Lateral Sclerosis" (Near-ALS) which got conditional approval after Phase 2.
- Ossron™, from **RMS (Sewon Cellontech)** an autologous MSC-derived osteoblast therapy for bone repair approved in 2009.
- Queencell®, from **Anterogen**, an autologous therapy for s.c. fat tissue repair.
- Rosmir®, from **Tego Science**, an autologous cell therapy approved in 2018 for the treatment of under eye wrinkles.

In July 2017 Kolon TissueGene a part of Kolon Life Sciences and its partner Mundipharm got approval for an osteoarthritis gene therapy, Invossa, but the Korean MFDS revoked the license in 2019 due to fraud. It was a big scandal once again shaking the ATMP community. In MFDS statement they said; "*One of the main ingredients of Invossa was identified as kidney cells (293 cells), not cartilage cells, and the data submitted by Kolon Life Sciences were found to be false*."

Furthermore, criminal charges were filed against Kolon Life Sciences.

The ministry was not so much concerned about the safety of Invossa, as no drug-related side effects were identified during the clinical trials.

Regarding the validity of Invossa, the results of the clinical trial itself were considered respectable. "*I believe the drug can alleviate pain and improve functions as have been verified through the clinical tests*," said Kang Seok-yeon, Director of biopharmaceuticals at MFDS.

In order to strengthen safety, QC standards will be prepared in all stages from collection of cells to processing, storage and supply. New regulations concerning the origin and

development status of cells in the R&D stage will be proposed by MFDS to further strengthen the quality and safety management of ATMPs. There will also be requirements to conduct new tests applying the latest analytical methods at the end of the development of ATMPs

In addition, if there is a possibility of cell mixing, companies will be required to submit the results of genetic systematic tests on the cells used for R&D and manufacturing. MFDS will require long-term follow-up investigations, including sales and administration details of ATMPs and registration of abnormal cases, after an ATMP has been approval.

Another scandal is not good when the industry finally had started to recover from the immense damage caused by the previous even larger scandal in 2006 with the fabrication of stem cell experimental data that was published from then professor Hwang Woo-suk at the prestigious top ranked Seoul National University (SNU).

Public opinions

Like in Japan South Koreans are proud of the advancements made in life sciences but by saddened by the scandals occurring again and again.

SME companies ("Bio-Ventures"), Industrial players, and domestic Big Pharma

Some of the companies involved in developing ATMPs are listed below, then there are also several companies applying stem cell s for "cosmeceuticals" – cosmetics with some pharmaceutical properties for beauty and anti-ageing applications like BioSolutions and

Anterogen, www.anterogen.com developing cell therapies, cosmeceuticals and umbilical cord blood cell banking.

BioSolutions, www.biosolutions.co.kr has two cell therapy products approved, one autologous and one allogeneic. The company was previously known as MCTT. BioSolutions have several programs in clinical trials and also pre-clinical development in skin disease, osteoarthritis. The company has launched some anti-ageing, anti-wrinkling and whitening cosmeceuticals on the Korean market.

GC Cell (formerly known as Green Cross Cell), the KOSDAQ listed ATMP focused company belonging to the Korean Green Cross Corp. or GC Corp. for short. The company has manufactured or expanded stem cells since 2007 and has a lot of GMP manufacturing experience. The company has a large pipeline of therapies in Immuno-Oncology, CAR-T and autoimmune diseases.

Recently GC Cell moved into new R&D laboratories next to Mogam R&D Institute at GC Corp. site in southern parts of Seoul.

Cha Bio & Diostech, http://en.chamc.co.kr/main.cha develops stem cell based treatments and is a part of the CHA Medical Group with clinics and, medical centres and hospitals as well as university and school of medicine.

Corestem, www.corestem.com was established in 2003 is public listed company developing stem cell-based treatments for rare diseases. It has one approved MSC therapy for ALS. Corestem has three programs in clinical development for CNS and autoimmune diseases. It's subsidiary ChemOn, www.chemon.co.kr/eng a non-clinal CRO and with a GMP manufacturing facility for cell-based therapies.

FCB Pharmicell; www.pharmicell.com established in 2002 got the world first MSC therapy for AMI approved in July 2011. The company have several programs in R&D and also offer CMO services.

JW CreaGene, www.creagene.com is a part of JW Corp., since 2009. CreaGene was established already in 1998 and is involved in cell therapy and anti-cancer vaccine development. Based on its success with CreaVax-RCC for renal cell carcinoma development is focused on hepatic cancer and brain cancer. The company is also developing a range of antigen and immune cell or stem cell cytokines. It has less than 50 employees and a turn-over of roughly USD7.6m in 2018.

Kangstem Biotech, www.kangstem.com is a stem cell therapy development company with three programs in early clinical trials or have completed Phase 1 studies a few years ago. Revenues comes from service and cell media business, as well as offering CDMO for cell therapies. Recently March 2019 Kangstem entered into an agreement with another Korean company, **SK Bioland** (www.skbioland.com) for marketing, co-development and manufacturing of the stem cell therapy, Furestem-AD, (a company in the giant SK chaebol, the third largest in Korea after Samsung and Hyundai) for atopic dermatitis received uSD13.2M in upfront payment.

Medipost (www.medi-post.com) has several stem-cell derived therapies under clinical development such as Pnemostem® for treatment of Bronchopulmonary Dysplasia (BPD) a paediatric disease, which has ODD in the EU and US. The drug candidate is also in development for various adult lung diseases.

Neurostem® is another stem cell derived therapy in clinical development (Phase 1/IIa in Korea as preventive treatment of Alzheimer's Disease, with USFDA trials being prepared.

Regenerative Medical Systems (RMS), www.rmsbio.net was established in 1996 and has developed three cell based therapeutic products, and has umbilical cord blood banking, not only in Korea but also in India, Japan, the Netherlands, Poland, and UK. It's one of the divisions (companies) of Sewon Cellontech Corp. (www.sewoncellontech.com).

Tego Sciences, www.tegoscience.com and www.tegocell.com, was established in 2001 and is public traded company on KOSDAQ. The company has autologous and allogenic cell therapies on the market for wound healing. The company offers CRO services and have several in-house development programs. The company has less

than 50 employees, with turn-over in 2018 of close to UDSD7M, which was a 9% decline from 2017.

Pre- and clinical development.

Several dedicated pre-clinical CROs for ATMPs could be found among the companies listed above. Furthermore, there are several state-of-the-art hospitals operating according to the highest Western standards.

Generally South Korea is a popular destination for Western companies to conduct regional multicentre studies as prices are lower than Japan and English ability is typically higher. Therefore most of the major MNC pre-clinical and clinical CRO:s are active in South Korea and they provides good bilingual services.

Manufacturing

Several of the cell therapy companies listed further above are also offering CDMO and CRO services, such as GC Cell based on its more than ten years GMP approval from KFDA at MFDS. Others are FCB Pharmicall, Kangstem, and Tego Sciences.

4.2. Bus. Dev. Considerations

Geographically and traditionally Korea is positioned halfway between China and Japan. They follow far eastern traditional and cultures, but with a lot of influence from US-style business and social practises.

South Korea is trying to be independent but are squeezed from many directions, US, China and Japan. This strife to be independent is reflected in the number of self-employed business that are roughly 10x larger than that of Japan.

Koreans' relationship with time is also a mixture between monochronic like in Japan and Chinese polychronic.

Korea is a high context culture, saying and acting indirectly. Top down decision making and very male dominated, more than Japan. However, English ability is often better than Japan.

Korean decision making is top down, with seniority and age being very important factors. Just as in Japan university ranking plays another important role. Thus, it is very important to establish contacts with a counterpart as high up in the organisation as possible. One shortcut would be using leverage from local / regional advisors and their networks.

South Koreans are often very well organised, just like in Japan.

Some say that South Korea is like Japan, but on steroids!

Low risk appetite and not willing to pay "bio dollars", but access to patients at lower cost than Japan, reimbursement and possibilities to create regional deals (ASEAN).

EuroStar R&D financing is possible in joint development projects with a local collaborator, as South Korea is one of the members states to the agreement. Furthermore, the Free Trade Agreement with EU also simplifies trade with South Korea. Additionally, the South Korean government have very generous grants and support structures in place for life science related R&D, and manufacturing. South Korea and Israel are the two top countries in the world in terms of R&D expenditures of GDP 2017, with 4.55% according to OECD data.

Some suggestions:

- When out-licensing to a South Korean company, investigate what risk : benefit and extra workload a regional deal including ASEAN would create?
- South Korean companies are rather active in some ASEAN countries like Malaysia, Vietnam, the Philippines, Thailand, Myanmar, Cambodia etc., which would open up additional possibilities to revenues, at least to Medical Tourism destinations such as Malaysia and Thailand.

Sometimes South Korean life science companies would invest in EU companies, while Korean investors would rarely go outside their comfort zone.

4.3. Regulatory Affairs & Custom control

Korean Food & Drug Administration (KFDA) was elevated to a Ministry in March 2013, called the Ministry of Food and Drug Safety (MFDS). Korea has been a member of PIC/S since May 2014 and ICH since November 2016. In 2017 there were roughly 1,800 employees at MFDS including all the regional offices, whereof 420 with National Institute of Food and Drug Safety Evaluation (NIFDS).

The MFDS has a regulatory structure in four levels. The base level (Level 4) is the Guidelines on the “Requirements for Quality Documentation of Cell Therapy Products” and the “Guidance on Sponsor-Investigated trials of cell Therapy Products for Academic Purposed, etc.”. The next level (Level 3) is the “Notification on review & Authorization of Biological Products”. Level 2 stipulated the “Enforcement Rules of the Safety of Pharmaceuticals” and the top level, Level 1 is the “Pharmaceutical Affairs Act”, the law. It contains:

- Rules of the safety of Pharmaceuticals (Regulation)
- Notice on the Approval of Pharmaceuticals (incl. biologics) MFDS Notices
- Interpretations of the law
- Legally Binding
- Guidelines for the Industry and Reviewers

The ministry has issued a series of guidelines pertaining to ATMPs such as QC, definitions used for cell- and gene-therapy in South Korea, Mycoplasma testing, pre-clinical assessments and testing of viral vectors etc. evaluation guidelines but many of them are in Korean. It’s not easy to find these guidelines in English.

MFDS could be reached at; https://www.mfds.go.kr/eng/index.do

MFDS may grant priority review and also issue conditional approval for cell therapy products used for life-threatening or severe irreversible diseases. A conditional approval requires post market confirmatory clinical trials. There are no exemptions in quality and non-clinical data. It's mandatory to hold scientific consultations with MFDS. The exploratory clinical trial should be:

- Well-controlled, randomized, blinded and comparative.
- Efficacy endpoint should use well-defined surrogate endpoint or intermediate clinical endpoint that represent confirmatory endpoint.

Marketing could only be made in designated hospitals. Any off-label use is strictly prohibited, and patient informed consent is required.

Post-marketing requirements:

- Conduct Phase 3 trial and write annual reports;
  - The trial design should be developed in close collaboration with the Cell- & Gene Therapy products Division of MFDS.
  - Design requirements; well-controlled, randomized, blinded and multi-centre, with an endpoint that reasonable predicts the stated clinical benefit.
- The time period determination would be based on prevalence of the disease, efficacy evaluation period and number of available patients.
- Regular report of risk management status.

Formal regulatory consultations are possible. The fees are low to moderate.

MFDS has an online application system www.ezdrug.mfds.go.kr and follows the CTD-format.

Import and export of blood components and tissue are regulated by the Human Tissue Act from 2017 with very strict regulations how collected tissue could be handled. It is currently not clear if any export of tissue samples is allowed from South Korea.

4.4. Price & Reimbursement

South Korea is promoting and prioritising cost innovative therapies moving away from generics. Every manufacturer must provide pharmacoeconomic evidence to show clinical - cost benefits, budget impact based on expected sales, international reference price and the general impact on public health to determine reimbursement.

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

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

- HIRA make an assessment within 150 days of application

- NHI determines the maximum price via negotiation within 60 days
- MoHW reviews and announces the price to the public within 30 days

The premium pricing level has been lower than Japan, but in some rare cases approved products in South Korea are selling at equal or higher price than US. However, there are mandatory price cuts every second year.

Price example of ATMPs (cell therapy products) approved and marketed in South Korea, shows low to moderate pricing:

- Caristem by Medport, USD 19,000 – 21,000
- Cupistem buy Anterogen, USD 3,000 – 5,000 per treatment
- Hearticelgram by FCB Pharmicell USD 19,000

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