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# Accelerated Access of Advanced Regenerative Therapies: an Industry Perspective

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The lengthening shadow of increase in health spending in the coming years is sharpening the minds of legislators, regulators and payers alike. The growing time-to-market, the rising costs in development of novel medicines, as well as the more basic drive to be 'ahead of the game', forces the industry and the legislators to rethink basic postulates of drug development. The global regulatory environment is undergoing major reshape, allowing patients early access to breakthrough technology and allowing industry opportunities for early access to market. Patient advocacy groups are incorporated in legislation discussions, and are brought into the room where industry and regulator discuss the clinical development of novel therapies. Earlier access to market allows smaller commercial companies to jump through the 'death valley' of drug development, reduce the traditional high investment risks in biotechnology, and ultimately provide more competition to big and well-established pharma giants.

**Submitted**: Apr 22nd 2018 ▶ **Published**: 7th July 2018

This article provides an overview of the current framework and established procedures for the regulation of regenerative medicines in Japan, Europe and the US. Legislation in these markets is galvanizing regulatory pathways for innovative technology in general, and regenerative medicine in particular, towards early access to market. Four such pathways in various stages of formation can be identified:

1. Facilitation of consultation, agreement and review processes with the regulator;
2. Increase reliance on the accumulation of "real-world" confirmatory evidence of efficacy

following initial marketing authorization;

3. Expanded access to treatment during advanced stages of development;

4. US law provides an additional unique benefit priority vouchers to novel products approved in designated fields of development. These vouchers can be then transferred for use by a third party, and are known to have a high market value.

## PMDA LEADING THE WAY IN REGULATION OF REGENERATIVE MEDICINE

The 2012 winning of Shinya Yamanaka for Nobel Prize in medicine has turned into a battle cry for Prime Minister Shinzo Abe, who won a landslide election victory that year. Just like in many other cases in the recent past of Japan, the revolution started from the top, with medical and healthcare industry being one of fields in focus [1]. In November 2013 the Diet, the Japanese legislature, passed the new Act on the Safety of Regenerative Medicine (ASRM), and the revised Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act), both coming into effect on November the following year [2]. In a stroke of a legislation act, these two pieces of legislation has turned the attention of the regenerative medicine biotech industry to Japan.

Abe government has set 7-year goals for this new regulation:

1. To apply new drugs developed by iPS cell technology to clinical trials;

2. To increase the number of approved cellular therapeutic products;

3. To expand the target diseases in clinical trials;

4. To develop equipment or devices related to regenerative medicine

While ASRM frameworks the legal conditions for the use of processed cells in the context of hospitals, it is the revision of the PMD act that drew the attention of commercial companies, interested in the development of regenerative therapies. This change in PMD act included a new chapter on "Regenerative medical products", defining them as processed human cells that are intended to be used for either

1. The reconstruction, repair, or formation of structures or functions of the human body; or

2. The treatment or prevention of human disease; or

3. For gene therapy.

This section of regenerative medical products in the PMD Act introduces a novel mechanism of conditional/time limited approval system for regenerative medicine in indications, where the PMDA determines there is an unmet need (but not necessarily of serious consequences). Unlike the case with FDA RMAT program, the determination for eligibility to be included in the program is done at a late stage, during the review process of the marketing application [3], although PMDA may provide tacit indication for the applicability of the development program to be accepted under the new legislation.


DOI: 10.18609/cgti.2018.055

The motivation for this new mechanism was the recognition of the unique difficulty for the collection and evaluation of efficacy data for regenerative medical products in a short time period, due to such characteristics as non-uniformity of product quality arising from heterogeneity of cell source, the limited number of patients available for clinical trial for some clinical unmet needs, and the practical difficulties of conducting controlled studies with these therapies [3]. The PMD Act facilitates an early access of Japanese patients to cutting-edge regenerative treatments, allowing companies to commercialize their treatments at an earlier stage of development, while shifting the confirmation of the product efficacy from premarket phase to a post-market commitment.

As the name suggests, the mechanism of conditional time-limited approval allow companies to commercialize regenerative therapies provided its safety is ensured and the results of clinical trials are considered likely to predict efficacy [4]. Following this conditional approval, the safety and effectiveness of the product is expected to be confirmed in conjunction with postmarketing safety measures, within a timeline of up-to 7 years, although the timeline for full marketing authorization is considered on a case-by-case basis. The likelihood of efficacy can be demonstrated in a Phase II study using an acceptable surrogate endpoint. Alternatively, the PMDA may accept a design of a study, powered to demonstrate efficacy in a clinically significant endpoint, but for an alpha value that is higher than the usual 5%. In addition, the program allows the conditionally approved products to apply for reimbursement in the universal health insurance system of Japan. Contrary to HTA bodies in Europe, the Central Social Insurance Medical Council, the governmental body in Japan, which determines reimbursement prices for the national health insurance (NHI) system, consider PMDA conditional approval as sufficient to pass the bar for the determination of reimbursement price. While many Japanese are covered by health insurance policies payed by their employers, the NHI provides a universal coverage of health benefits for all citizens and permanent residents in Japan, with a co-payment policy ranging between 10–30%.

Until today, one product has been granted conditional and time-limited authorization, based on the probable benefit that was demonstrated by pilot open-label clinical trial of 7 patients with serious heart failure. The Terumo Medical product, named "HeartSheet", is an autologous skeletal myoblast cell sheet. It has been authorized for a 5-year conditional approval period for use in patients [5]. As the conditional time limited marketing authorization law stipulates, the use of heartsheet is restricted to qualified physicians and facilities. All treated subjects are subject to mandatory postmarket surveillance. In order to gain the full marketing authorization, the product must show evidence of efficacy in 60 cases treated with the product, and additionally must show that the product yields greater clinical benefit than that achieved by 120 control cases treated with the current standard of care. Interestingly, the Central Social Insurance Medical Council has fixed a high price

for Terumo Hearsheet ($122,000 USD), signaling biotechnology industry of its high willingness to pay for innovative technology it consider promising, and taking upon itself the added risk of uncertainty of novel technologies with limited proof of efficacy. One question remained to be answered, with regard to this program, is how sponsors will deliver the necessary bias-free confirmation of efficacy in a post marketing setup, given the obvious difficulty in the conduct of randomized clinical studies after marketing [6]. Beyond the requirement of this legislation for post-marketing studies to be conducted according to Good Post-marketing Study Practice [3], the specifics is left for discussion between the sponsor and the PMDA. It may be the moment in the history of medicine, where large datasets of real-world observational evidence wins its place as a gold standard of evidence-based medicine, and an alternative to the much-appreciated randomized control studies.

## EMA EXPLORING THE IDEA OF ADAPTIVE PATHWAY

In its 2010 strategy statement "roadmap to 2015", the EMA has pointed out that it wishes to refine the use of its conditional marketing authorization, as well as to explore the possibilities of a "staggered" approach towards marketing authorization of new medicines, making use of real-world data to broaden the indicated treatment population post-authorization [7].

Living up to its statement, the EMA has launched early in 2014 an "adaptive pathways" pilot program. The program was chartered to further explore how existing regulatory tools at the hand of EMA may assist the streamlining of development and ultimately stimulate industry interest in areas of unmet medical needs/neglected and rare diseases. Although not specifically geared towards ATMPs, three of the 18 products that the pilot program selected for in-depth discussion were cell or gene therapies, including PLX-PAD of Pluristem and Lentiglobin of Bluebird Bio (third company remained anonymous) [8].

The adaptive pathways pilot was not greeted by all [8]. Criticism from within the EMA, as well as from health technology assessment bodies and payers, concentrated around the fear that an adaptive pathways program in the EMA will reduce the strength of evidence required to support the safety-benefit assessment. As lack of demonstrated efficacy is the most frequent reason for failures in late-stage development, discussion on adaptive pathway approach often revolves around the type, strength and quality of evidence of efficacy required in order to allow the first marketing authorization. Especially in European setting, this discussion bears weight for commercial companies, as technology appraisals by HTA bodies and reimbursement decisions by payers are expected to be affected by the amount of evidence of efficacy, regardless of the marketing authorization provided by the EMA. Parallel scientific advice procedure, between EMA and selected HTA bodies may bring companies to early awareness of the type of issues they may face with technological appraisal down the road.


DOI: 10.18609/cgti.2018.055

A second source of controversy around the adaptive pathways approach relates to the expected use of real world evidence post-initial marketing authorization, for the support of subsequent expansion of indication. Real world data is currently in use in the EMA, for the assessment of safety signals, restriction of indications and the withdrawal of marketing authorizations in case of unfavorable safety findings. However, observational data is much more controversial when it comes to its use for the confirmation of efficacy (as opposed to the generation of hypotheses). Causal inference from observational data may be difficult in most situations as it is open to alternative explanations.

The use of randomized controlled studies, following initial marketing authorization, either for the confirmation of efficacy or for the further expansion of indication may also prove to be challenging. Patients and physicians may be reluctant to sign up for a placebo controlled study where it can be accessible by either on-label or off-label prescription. Geographical phasing of marketing, i.e. marketing the product in one geographical area while performing study in an RCT in a second geographical area, can be a solution to this problem, but may not necessarily be appealing from a business perspective.

The pilot program of Adaptive Pathways gave the necessary input for the Priority Medicines (PRIME) program, that was launched in 2016. It is aimed to provide early, proactive and enhanced support for sponsors of novel medicinal products that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. As in the case with Adaptive Pathways, the stated goal of this program is to help patients to benefit, as early as possible, from therapies that may significantly improve their quality of life. By the end of 2017, 41% of all products granted PRIME designation were either cell or gene therapy products [9].

## CAT CERTIFICATION PROCEDURE

The Committee for Advanced Therapies (CAT) is the responsible body at the EMA for the assessment the quality, safety and efficacy of ATMPs. A unique service the CAT is offering to small and medium size enterprises, that are engaged in the development of ATMPs is the process of Certification. This process is akin to a mock submission of a marketing authorization application (MAA) for the quality section, or, if the company chooses, to the quality and non-clinical sections of the MAA. Contrary to a scientific advice, the CAT is not challenged with specific questions, but is required to evaluate the entire dossier and express its opinion over it.

The certification procedure aimed to provide the SMEs with a non-binding certification on the adequacy of development, allowing it to communicate it to potential partners and investors. Furthermore, it provides a written CAT opinion and an evaluation report that includes a list of issues. This may be a strong benefit for SMEs that are struggling to map the deficiencies they need to gap towards MAA and sets, even if not officially, a first draft of understandings and issues for further

discussion with the EMA, to consider prior to MAA.

Interestingly, the CAT may choose, as part of its certification process, to send GMP inspectors or GLP monitors to a site visit, prior to its evaluation report. Although not a formal inspection procedure, the possibility of a visit by a GMP inspector, sent by a regulator, while clinical studies may be running in EU member states, can be a strong repellent reason against going for this procedure, even in companies that have high confidence in their quality assurance system in place. This may be a reason why, since 2009, only 11 companies turned to CAT for this procedure [10].

## 21ST CENTURY CURES ACT

The FDA has traditionally avoided from setting different rules for the clinical development of advanced therapies. The Office of Cell, Tissue and Gene therapies (recently renamed the Office of Tissues and Advanced Therapies; OTAT) was establish in order to accumulate and develop the expertise in the evaluation of the quality and non-clinical data of advanced therapy, but there was no published policy regarding any unique approach the FDA is taking in the evaluation of clinical data for advanced therapies. It was a matter of a determination of case-by case standards.

The 21st Century act was enacted in the last days of the Obama administration. It contains various measures that are aimed to boost research and development for innovative technologies, and find a solution for the opioid abuse epidemic. In its Section 3033, it establishes with what will be known as regenerative advanced medicinal therapy (RMAT) designation, and in its Section 3034, establishes a legislation to simplify regulation on devices in regenerative therapy.

The purpose of legislators in legislating the "Accelerated approval for regenerative medicines" was just that – to provide an accelerated path for the development of regenerative therapies, amounting to a type of conditional marketing authorization. Intentions aside, the RMAT designation is highly similar to the well-established breakthrough designation, at least in the features it offers to those who hold it [11].

A significant difference between the two, apart for the obvious technological requirement of being a regenerative medicine advanced therapy, is in the list of qualifying criteria. While breakthrough designation require preliminary clinical evidence which indicates that "the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies", the parallel qualifying criterion for RMAT designation only requires that preliminary clinical evidence indicates that "the drug has the potential to address unmet medical needs for such disease or condition". In effect, this means that products at initial stages of development, that have good preliminary evidence obtained from non-controlled studies, but with good historical controls, or from well-designed retrospective studies, that had no chance in getting breakthrough designation, may receive the RMAT designation. Until June 2018, 20 products have received the RMAT designation, out of 64 applications [12].

Just like in the case of breakthrough designation, the RMAT


DOI: 10.18609/cgti.2018.055

designation is primarily an invitation for discussion. It grants the holder the possibility to conduct an Intensive discussion with senior managers in the FDA on efficient drug development, mainly actions to expedite development and review. On top of the general means to expedite development, such as the use of surrogate endpoints and intermediate clinical endpoints, the RMAT designation allows to consider accelerate approval based on reliance on clinical studies that are conducted on a limited number of clinical sites.

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