

PRODUCT DEVELOPMENT

Regulating regeneration in Europe

BY LAUREN MARTZ, ASSOCIATE EDITOR

As Europe rethinks its policies on regenerative medicine, the question is whether it can regain its footing in a competitive field it once led, given the in-built inconsistencies across the EU's member states.

Europe positioned itself early as a leader in regenerative medicine, but the different protocols, requirements and practices between European member states have made the region less attractive for developing regenerative medicines, according to six regenerative medicine company executives who spoke with BioCentury.

From 2009-2015, Europe and the U.S. produced roughly equal numbers of newcos in the field, based on seed and series A financings (see Figure: "Generation Regeneration"). In all disease areas, Europe was less than half as active as the U.S. in raising seed and series A rounds in the period, meaning it relatively outperformed in regenerative medicine.

The picture reversed in the last six years, when the number of U.S. regenerative startups spiked, and the number in Europe progressively decreased.

The peak year so far in the U.S. was 2017, when 14 regenerative medicine companies raised seed or series A funds, compared with two in Europe, according to BioCentury's BCIQ database. This year has so far seen four companies in the U.S. and a single one in Europe — Cell Mogrify Ltd., which spun out of Cambridge University with \$3.7 million seed funding.

To stay globally competitive, EMA and the European Commission are re-examining a suite of regulations.

On the table are unified clinical trial systems across Europe and new guidelines to encourage consistent interpretation of laws affecting regenerative medicine by member states.

Fragmentations across EU member states may be a bigger obstacle than the differences between regulatory pathways in Europe, the U.S. and Japan, said Miguel Forte, CEO of Zelluna Immunotherapy A/S and COO of the International Society of Cellular Therapy.

As CAR T therapies and gene therapies become increasingly central to drug developers, Europe could see its ability to compete weakened by the hurdles it has created.

Fragmentation fix

Inconsistent enforcement and interpretation of EU laws and guidelines from one country to another has made it difficult to coordinate cross-border clinical trials and mount commercial campaigns, lowering incentives to develop and sell regenerative medicines in Europe.

"WHAT IT BOILS DOWN TO IS HOW EACH AGENCY WORKS."

MIGUEL FORTE, ZELLUNA

While the need for separate approval to conduct clinical trials by each country applies to all therapeutics, the situation for regenerative medicine is exacerbated by inconsistent laws governing the use of GMOs.

Each member state has its own application and approval process for therapies consisting of or containing GMOs. The result is that companies with gene therapies or genetically modified cell therapies need to go through a separate process in each country.

"The fractionated approach across the EU on things like GMOs and how they are regulated is a delaying obstacle and something that can cause a very negative impact on speed of getting into the clinic," said Forte.

EMA and EC are working on a solution. In 2017, EMA and EC's Directorate-General for Health and Food Safety (DG SANTE) published a joint action plan to foster development of Advanced Therapy Medicinal Products (ATMPs).

The plan details 19 actions to address shortcomings in the regulatory environment for ATMPs including the interplay between GMO and medicines legislation.

Several of the points in the plan have been addressed with new guidelines, including a revised procedure for ATMP assessment and a guideline on manufacturing protocols, but work to resolve the GMO issue remains underway.

Hospital exemptions are another problem the plan aims to fix.

In Europe, hospital exemptions were introduced as an exception to the centralized marketing authorization requirement for ATMPs.

EU member states are allowed to permit the use of ATMPs that are custom-made for a specific patient, prepared on a non-routine basis and used in a hospital setting. This applies to autologous therapies or and certain allogeneic cells administered on a patient-by-patient basis.

Like FDA's right-to-try legislation, hospital exemptions provide patients with access to unapproved therapies when there are no other options, but the ATMPs used under hospital exemptions are one-off treatments that don't come from company pipelines. The U.S. does not have an equivalent.

The law was designed to "provide a life-saving last hope for patients," said Forte, but some stakeholders think it could hurt patients in the long run by discouraging development of ATMPs through the proper channels.

The argument, said Annie Hubert, senior director of European public policy, is that hospital exemptions decrease the already small number of patients available for clinical trials and, in some cases, allow unauthorized compounds to compete with marketed products. Hospital exemptions are also handled inconsistently across member states, adding further complexity to development plans.

"The usage of that mechanism becomes a problem when it is the preferred option over an industrially developed product," added Forte. There are examples of marketing failures due to competition with unauthorized products, especially in countries like Germany where hospital exemptions are frequently used, he said.

Still, he thinks "hospital exemptions and industrial development can live together without negative impacts in most cases."

While the ATMP action plan aims to home in on the best use of hospital exemptions, "unfortunately we've seen very little progress on that point," said Hubert. The Association for Regenerative Medicine (ARM) has provided the EC guidance and proposed solutions for the hospital exemption and GMO issues in position papers.

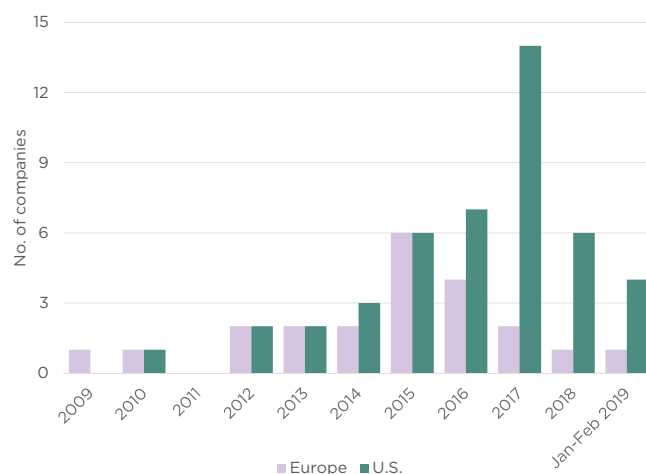
The EU is also working to promote ATMP development via other mechanisms.

For example, the European Commission's Horizon 2020 program is funding several projects involving ATMPs, and the Innovative Medicine Initiative (IMI) launched calls around ATMPs earlier this year.

This week, the EU Council and Parliament announced that next phase of the Horizon 2020 research program, Horizon Europe, will be funded

Regenerative medicine company formation

Europe positioned itself as a leader in regenerative medicine 10 years ago, but the U.S. has taken over the top spot for therapeutics development since 2016. The chart includes cell and gene therapy companies that raised seed or series A rounds since 2009. Companies that completed both rounds during the period were only counted for the first financing. While Europe usually has less than half as many new company formations each year as the U.S., Europe held steady with the U.S. in regenerative medicine companies with seed and series A rounds through 2015. The chart includes active companies developing cell and gene therapies, and excludes supply/service companies and those that have been acquired or ceased operations. Source: *BCIQ: BioCentury Online Intelligence*



through 2027. The EU Council proposed a €100 million budget, which hasn't yet been accepted.

Accelerating regulation

The jury is out on whether differences between the regulatory pathways between Europe, Japan and the U.S. will stop Europe from catching up.

Last July, EMA reported that 36 of 177 (21%) requests for PRiORity Medicines (PRIME) eligibility were accepted since introduction of the designation in 2016. About 30% of PRIME-designated therapies are ATMPs, according to Hubert.

In the U.S., 30 of the 91 requests for Regenerative Medicine Advanced Therapy (RMAT) designation (33%) had been accepted as of February 1st. RMAT was introduced in 2017.

In common with RMAT and Japan's Sakigake, Europe's regulatory pathways for regenerative medicine cover a wide variety of gene, cell and tissue-based therapies, not just ones that regenerate lost cells. The reason is that many of these therapies are likely to have disease modifying

effects in areas of unmet need, and could benefit from a high degree of interaction with regulators due to their complexity.

“I think the pathways are pretty comparable. They each have the same intention and give the opportunity to expedite the discussions. What it boils down to is how each agency works,” said Forte.

Sakigake, RMAT and PRIME all offer early interactions with regulators and priority review. Many products with the designations are also eligible for accelerated approval.

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Shaun Stapleton, head of regulatory affairs at ReNeuron Group plc., a U.K.-based regenerative medicine company, said that Japan makes it much easier to obtain conditional approval. Sakigake allows it, “after just an initial suggestion of efficacy and a read for safety,” said Stapleton.

Caladrius Biosciences Inc.’s VP of Global Regulatory Affairs William Sietsema agreed, noting that products can get conditional approval in Japan based on very limited Phase II datasets.

In December, Japan’s Ministry of Health, Labor and Welfare (MHLW) granted condition approval to the cell therapy Stemirac based on clinical data from 13 patients. Stemirac is an autologous bone marrow-derived mesenchymal stem cell treatment for spinal cord injury developed by Nipro Corp. and Sapporo Medical University.

Caladrius’ CD34+ cell therapy CLBS12 has Sakigake designation in Japan, where it is in Phase II testing to treat ischemia/reperfusion injury. Its lead candidate CLBS14, another CD34+ cell therapy, has RMAT designation in the U.S., where it is in Phase III testing for angina. ReNeuron’s CTX stem cell therapy is in Phase II testing to treat ischemic stroke in the U.S. It does not have RMAT designation, and is not being developed in the EU.

RMAT stands out because it allows inclusion of real-world data in conversion to full approval, rather than only clinical trial data.

This difference could save companies time and money, although the pathway’s newness means it isn’t yet clear how much real-world data FDA will accept.

“We haven’t seen an RMAT-designated product get to the market yet, so while this is a great perceived benefit that draws many companies, we don’t know how much real-world data will actually be used,” Stapleton said.

Celixir plc CEO Ajan Reginald told BioCentury another benefit of RMAT is that it can allow conditional approval based on a surrogate endpoint that is “reasonably likely” to predict clinical benefit but hasn’t been fully validated through clinical trials. That’s particularly valuable in cardiovascular diseases, he said.

“In heart failure, usually you have to use a mortality endpoint that will take years to read out. That’s not sensible or necessary for regenerative medicine, where we know that LF fraction or size of scar are directly related to mortality. RMAT may allow us to shorten trials by using a shorter-term endpoint that indicates regeneration,” Reginald said.

LV ejection fraction and size of scar are not included on FDA’s table of surrogate endpoints that were the basis of drug approval or licensure.

Celixir’s cell therapy Heartcel is in Phase II testing in the U.S. to treat ischemic heart disease. The company is in the process of applying for RMAT designation.

“RMAT looks like a game changer. We’re super excited and are following the pathway ourselves because there are so many clear advantages. It’s clever, sensible and appropriate for cell and gene therapy,” said Reginald.

EMA’s conditional marketing authorization does not allow use of real-world data but does allow surrogate endpoints.

However, the stakeholders interviewed by BioCentury failed to identify any unique advantages to the European pathways.

While ARM says that EMA and the EC are taking the right steps, none of the CEOs saw any reason to prioritize Europe for development of regenerative products. But they still saw Europe as an important market, and would likely develop products there after first launching in the U.S. or Japan.

In 2014, EMA conducted a pilot study of the adaptive pathways concept that could put European regulation on par with FDA’s RMAT by allowing approvals in stages, beginning with a restricted patient population, the use of surrogate endpoints in early data for conditional approval and real-world evidence to supplement clinical trial data.

EMA has not issued any updates since 2016. ■

COMPANIES AND INSTITUTIONS MENTIONED

Caladrius Biosciences Inc. (NASDAQ:CLBS), Basking Ridge, N.J.

Cell Mogrify Ltd., Cambridge, U.K.

Celixir plc, Stratford-upon-Avon, U.K.

European Medicines Agency (EMA), Amsterdam, Netherlands

Nipro Corp. (Tokyo:8086), Osaka, Japan

ReNeuron Group plc (LSE:RENE), Bridgend, U.K.

Sapporo Medical University, Sapporo, Japan

University of Cambridge, Cambridge, U.K.

U.S. Food and Drug Administration (FDA), Silver Spring, Md.

Zelluna Immunotherapy A/S, Oslo, Norway