Ana Hidalgo-Simon â?? Head of Advanced Therapies, European Medicines Agency

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The EMAâ??s Head of Advanced Therapies Dr Ana Hidalgo-Simon outlines Europeâ??s evolving regulatory framework for regenerative medicines, how it differs from those in the USA and Asia, ethical and pricing challenges, and why global regulatory harmonization and collaboration is crucial.

Ana, could you start by introducing your background and your current role as the Head of Advanced Therapies for the European Medicines Agency (EMA)?

I am a medical doctor and I did my PhD on cell-preservation in the context of organ transplants, specifically endothelial cell preservation, at the University of London, so I have had a long-term interest in cell therapy and how to work with cellular elements within the body. I have been with EMA for over 17 years now, beginning on the pharmacovigilance side. Six or seven years ago, I moved to the development side, supporting scientific evaluation as head of the specialized scientific disciplines department, particularly in aspects like pharmacokinetics and biostatistics.

In my current position, I head the Office of Advanced Therapies, which is a relatively new office, established in March 2020, although it builds on EMAâ??s 20 years of experience with cell and gene therapies. The pace of such advanced therapies has really picked up in recent years, with a

significant number of submissions and a lot of scientific advice. As an indication, over the past ten or 12 years, we have had 17 advanced therapies approved. Now, we are expecting to approve ten or 12 new advanced therapies *each year* for the next few years. That is a dramatic increase.

This is why EMAâ??s previous director decided to start the Office of Advanced Therapies, which uses a matrix set-up within the agency and boasts a very multidisciplinary team. In many ways, advanced therapies cross two dimensions: therapeutic areas and agency functions. Advanced therapies do not confine themselves to any specific therapeutic areas, and there are essential clinical and non-clinical elements to consider. There are many methodological challenges. Therefore, while the knowledge and expertise regarding advanced therapies already existed within EMA since we have been dealing with these products for more than a decade, the decision was made to take a more holistic approach, and to give them extra support.

This also gives us the platform to communicate more closely with stakeholders and partners. Advanced therapies are in the spotlight these days, and we need to work closely and transparently with stakeholders, including academics, researchers and patients, as well as SMEs and large pharma, of course.

In countries like the US, the work on regenerative medicines has really been driven by the 21st Century Cures Act, which outlined a clear direction for the US FDA. What are for Europe the guiding principles of your work here at the Office for Advanced Therapies?

As you alluded to, the systems in the US and Europe are completely different, to the point that even the definitions for these therapies are different: regenerative therapies versus advanced therapies. Our legislations are also different.

The basic principle is that we want these medicines to be used by the patients, not merely available in the market. That is quite a departure from the traditional approach where regulators would not worry about the commercial viability of a product. However, for advanced therapies, market approval is not the end of the journey, and we really want to reach the final destination, which is having patients benefit from these therapies. Access is fundamental.

The other aspect of advanced therapies is that we realized that we need to engage and work with academics a lot more because many of the ideas and initial research actually come from that community, who have not traditionally been commercial drug developers. Therefore, they are less familiar with the regulatory and clinical development processes, the post-authorization requirements, large-scale clinical trials, etc. At the same time, because patients are more involved in the development, there is a seminal role for them to play as well. Even before the formation of the Office for Advanced Therapies, EMAâ??s Committee for Advanced Therapies (CAT) included patient and healthcare professional representatives as full members, with full voting rights.

At EMA, among other incentives and support tools for developers, we have the PRIME scheme, which is intended to enhance the support for the development of medicines that target an unmet medical need, including but not limited to advanced therapies. However, due to the revolutionary nature of advanced therapies, we have noticed that around half of all PRIME products are now advanced therapies, and this is because the scheme works very well for these advanced therapies, facilitating early dialogue and scientific advice, with numerous benefits for sponsors. For instance,

we appoint a rapporteur from the Committee on Advanced Therapies to provide continuous support, and we also provide scientific advice at key development milestones.

What are some of the main ethical challenges your office has faced in regulating advanced therapies?

One of the main issues is how to deal with out-of-specification therapies, i.e. when an advanced therapy presents one or more parameters that fall outside the authorized specifications. This is not an uncommon occurrence. The ethical dilemma is that you have a product that falls outside established parameters, but has been produced using the patientâ??s own material, and sometimes the patientâ??s condition is so severe that they are running out of time. The argument is whether the product should be used on the patient anyway? This is a very difficult choice, and it requires a dialogue between the patient and their doctor, certainly. From our side, we are always trying to avoid this scenario, and we work with sponsors closely to ensure that we define the best product specifications. We cannot have specifications so tight that products fall out of them frequently and materials are wasted but we also need to ensure that we have efficacious and safe therapies. At the end of the day, we need to set some parameters â?? and to do that well, we have to work very, very closely with all the stakeholders.

One of the interesting features of these advanced therapies is the importance of manufacturing to the process of development, since the process *is* the product. Is that something that falls under the purview of EMA?

Certainly, we focus as well on the quality and consistency of the manufacturing to ensure that the therapies are safe for patients. The major issue here is comparability, because as you highlighted, the process is critical, and because this field is new, the manufacturing process is changing all the time, which is good, but these are also often very small batches because the patient populations are so small. We understand that. But these changes also need to be made in an extremely controlled and recorded manner so that we can evaluate and compare processes and so that we can use all the data collected linking all stages of development to the final product. That is important.

This is something that the smaller companies and academic developers are less familiar with. Pharma companies are well-acquainted with this process but not the newer and smaller players, so again, we are learning here to pass the message and to work with them closely.

With how new this field is and how quickly it is advancing, how does EMA stay on top of all the new developments?

Firstly, we draw upon all the national experts that are exploring these areas. Their systems and processes are not uniform, but they are working with their own national experts and academics, and our committees draw representatives from each country to bring all of their expertise together. The work of EMA is very much of coordination, alignment and compensation, and through that, we have insights into the upcoming and ongoing innovations.

For instance, we know that gene therapy is rapidly dominating this space, and we have access to a lot of scientific and academic advice and research. We also see that many new innovations, for instance, like drug-device combinations and health wearables and so on, no longer fall into clear-cut

categories of drug, device or other. The field is evolving, and the boundaries are blurring, so we are also preparing for this, partly through the recruitment of experts â?? though not so much now due to the COVID-19 situation â?? and partly through our dialogues and exchanges with national regulators, who are themselves exploring these areas.

There are many players in these new areas, from Big Pharma companies to small- and medium-sized enterprises, many of whom are spin-offs from academic and research institutions, so in that context, working with academics and other experts also helps us avoid duplicating research or reinventing the wheel. Through all these efforts, we have become much better at outlining and anticipating the regulatory science for these new areas. We also have our regulatory strategy to 2025, at EMA level and soon at EU level, overarching all national agencies.

You highlighted that access is fundamental for the Office when it comes to advanced therapies- to avoid approving therapies that then never reach patients. Since in Europe it comes down to the national health systems and payers when it comes to pricing and reimbursement, is there any means of coordination regarding access to approved therapies?

Access and affordability are fundamental worries for patients. The new Executive Director of EMA, Emer Cooke, has made it clear in her initial weeks that these are our main concerns. Traditionally, indeed, pricing and reimbursement are not responsibilities of EMA because these are set by national authorities. But we have started to have conversations with various stakeholders, including HTAs and payers at the EU level. Actually, this work began a few years ago. The idea is that the systems in these countries are already quite scattered, but we can help in certain ways. For instance, we spoke to the European Network for Health Technology Assessment (EUnetHTA) about the kind of information they need to make their decisions, so we could discuss how we could align our requirements. This would help drug developers and sponsors collect and arrange their data in an efficient way that would still meet all of our needs at the same time. We cannot just think about ourselves in isolation, we are pieces of a larger puzzle.

We need to rethink the system to ensure not only that a medicine is approved but also that it stays on the market. There have been cases of advanced therapies, approved ten years ago, that were no longer available because the manufacturer considered them no longer commercially viable. We have to work harder to ensure that these therapies ultimately reach the patients.

In terms of coordination, data is also a key component. When we spoke to Dr Janet Woodcock at the US FDA Center for Drugs Evaluation and Research, she was actually quite envious of the data quality and uniformity available within the European Union. Do you see this as a particular strength of the region?

Certainly, especially in some EU countries, I think there are very good and homogenous data within traditional healthcare systems, including registries since the majority of people would be covered by universal national health systems that have often existed for decades. That is a valuable resource. However, when you start going into the details regarding reimbursement and payments, there is not as much homogeneity so there is still room for improvement. We would like to improve this aspect further.

Patients actually play a crucial role in this, because they are the ones that are demanding change from the user side. They want us to get it right.

In addition to the US and Europe, Asia is also becoming a hotspot for advanced therapies, but the regulatory science in that region is not as harmonized with that in North America or Europe. Do you see increased global regulatory harmonization as important for the development of the overall advanced therapy field â?? and for Europe?

Absolutely. This is something that sponsors constantly speak to us about, and we are definitely moving towards that. However, this is not going to be easy because all these regions are not starting from a blank slate, they already have their own established systems that differ, sometimes significantly. No regulator can step in and say, change how things are done. Also, it is not always clear which is the right way of doing something. The European system is very much based on consensus, but we have a committee of 27 member countries, all with their own interests and systems. Therefore, our machinery is one of consensus and sometimes moves slower than we would like, but at the end of the day, it generates extremely solid decisions that take into account different perspectives. The US FDA, on the other hand, is a single institution representing a large country, so it has significantly more autonomy in its operations and decision-making.

However, global regulatory harmonization is key in advanced therapies because we are looking at patient populations that may comprise only a few hundred in the entire world. In general, in any case, drug development is so global these days. We have to work with our fellow regulators globally, and we are already doing so, of course. EMA accepts dossiers with clinical data outside of Europe, as long as they meet our regulatory standards. We are not lowering the bar, certainly, but we do offer flexibility. We are still not at the point where one single dossier can be accepted by multiple global regulators, but we are in conversation regarding more regulatory alignment.

This is also important because we have noticed that clinical trials for advanced therapies have increased significantly in Asia and North America, but they are not growing here in Europe. This is worrying because we want to foster the right R&D and clinical environment of the development of advanced therapies. We have a great research and academic ecosystem and we do very well in basic and early research, and of course, the European Commission has invested a lot in scientific research. for example, with the Horizon 2020 initiative. EMA also leads in terms of approvals of advanced therapies, so we are constantly accumulating experience.

It is the middle part â?? clinical trials â?? where we do see a need for improvement. We need to look into why it is difficult for companies to conduct clinical trials in Europe. Some of that comes down to the different regulations and systems across our member countries.

2020 has been an interesting and unpredictable year. Do you have a final message to send to our international audience?

COVID-19 has added an extra layer of uncertainty that we did not need, but even assuming that the pandemic resolves itself in a year, we will not return to the â??oldâ?? normal â?? and maybe we should not. It is normal when a crisis like this happens, we take a big hit and we have to rethink. All these changes that have happened as a result of COVID-19 are going to affect not just advanced therapies but the entire industry, and even society and life as a whole.

I do want to encourage sponsors and companies to continue knocking on our doors and to suggest improvements and changes we can make. We are operating in a global environment, these new developments and therapies are the future, and we cannot be fragmented, whether at the top level across international regulators, the second level *within* Europe and the European Union member states, and the third level across all stakeholders, including academics, large and small pharma

companies, patients, and so on. We need to think and work together and have everyone sitting at the same table in order to ultimately deliver to the patients the therapies they need.

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