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Speaking exclusively to PharmaBoardroom, the EMA's Head of Advanced Therapies Ana Hidalgo-Simon discusses steadily growing numbers of regulatory applications in the advanced therapy field, the vital importance of patient group insights, RWE collection and curation, hospital exemptions, manufacturing challenges, and more.

Although the European Medicines Agency (EMA) has been assessing and approving advanced therapies for over a decade, the Committee for Advanced Therapies is about to celebrate only its second birthday. How is the office structured today and what actions have been undertaken to ensure it is fit for purpose?

EMA's Committee for Advanced Therapies (CAT) has been in place for over 12 years, but the creation of the Advanced Therapies Division in April 2020 gave a clearer external signal of our commitment to advanced therapies. There is no single unified way of working in such a complex field, so a matrix organisation with very strong coordination has always been key; the fact that the office appeared on the EMA organigram two years ago is just part of a normal evolution in the support provided.

There are two main aspects to consider in advanced therapies. The first is cross-indications, which are much more numerous than for traditional medicines. The second is the high level of multi-

factors and multi-disciplines involved, with greater amounts of data being inputted around quality, post-authorisation real-world evidence (RWE), registries, and other sources. Additionally, having three committees rather than two creates additional complications, as does having both orphan and paediatric elements.

Have you seen rising numbers of regulatory applications for advanced therapies over the past two years?

Yes, and this growth can clearly be seen in the amount of scientific advice being given and the number of Innovation Task Forces (ITFs) meetings supported. However, while application and approval numbers *are* both rising, the pace at which they are doing so is slower than we had anticipated. Directors at EMA and other key regulatory bodies such as the US Food and Drug Administration (FDA) were predicting between ten and 12 advanced therapy approvals per year in the early 2020s. We are not yet seeing these numbers, which reflects how difficult these products are to develop, how many hurdles there are to overcome, and – of course – the slowing effect that the COVID-19 pandemic has had.

This steady growth is welcome as the system was perhaps not yet ready to deal with a sudden explosion of submissions and associated surge in workload. These therapies are complex, difficult, and have a huge public health impact, which means that the development and approval process is long and challenging.

How is the Committee for Advanced Therapies incorporating input from patient groups, and what lessons are you drawing from these inter-stakeholder interactions?

The fact that patients are getting both more sophisticated and more involved is a very welcome development for EMA. They have been part of the CAT from the beginning and are not just passengers but full members. Patient group representatives have full voting rights within the Committee and actively contribute to our discussions on everything from scientific advice to classifications and certifications.

Representatives of patients groups also act as our loudspeakers outside of the Agency, communicating both within their own associations but also with other associations outside their

disease areas. They go to conferences, are involved in our teaching exercises, and contribute to the regulatory documentation that the Committee produces.

There are many more patient groups today than five to ten years ago. How do you handle this from a regulatory perspective and what would be your suggestions for patient groups to reach a level whereby they can have a seat at the table?

There is a pyramid of associations at the regional, national, and European level – and we engage with the top level. We also talk with the relevant patient associations for the therapies being evaluated before attempting to answer a set of questions: what do you need, what can you offer, how can we train you, and what would you like to see more of?

We have a good structure whereby any association that wants to get involved can be directed to the right channel . When we have, for example, an important meeting for which participation is limited, we go to the European association, which then goes to its members and selects the most suitable participants. These participants are always a mix of those who are best prepared and positioned to have a good input, but also those who are willing to put in the time, effort, and energy needed.

EMA is extremely grateful for the participation of such groups and the point of view that they bring is very valuable. The input of those actually suffering from a disease themselves – or from the partner or parent of such a patient – allows us to spot issues that we may otherwise miss and is a fundamental part of our decision-making processes today.

Most of the advanced therapies currently available in Europe have been approved under the EMA's 'PRIME' scheme, but for fully-fledged approvals the agency is requiring 15 years of RWE. Both patient groups and initiatives like Go-CART have raised this as something of a barrier to access, what is your take?

To clarify, PRIME is an EMA scheme to enhance support for the development of medicines that target an unmet medical need, so these therapies can reach patients earlier. ATMPs represent nearly half of the products that have been granted a PRIME designation as disruptive technologies that have the potential to be truly game-changing for patients.

However, because of the uncertainty surrounding the long-term effects of these therapies, we require significant post-authorisation commitments. In contrast to chemical medicines – which EMA approves with a lot of confidence and for which there are thousands of patients in clinical trials – there is a huge amount of uncertainty around ATMPs. There are relatively few participants in clinical trials for these therapies – many of which treat rare diseases – and blind randomised trials are not possible. While not all ATMP approvals are conditional, given the reduced level of evidence available, it makes sense to take a more cautious path.

This cautious approach involves very clearly defining the patient subsets that will benefit from a particular ATMP. In complex fields, such as gene editing and modified bone marrow stem cell transplantation, we must define indications where there is good evidence that a therapy will be effective. For this reason, many of these therapies are indicated for very well determined groups of patients with a genetic variation that can be measured. Additionally, given that many of these therapies are being administered as a one off ‘cure for life’, long-term data requirements are crucial. Expanding a therapy out to wider patient populations requires even more data.

The 15-year requirement was chosen as it represents a decent period for tracking the effects of a treatment. If no detrimental side effects have been detected over a 15-year period, we can be reasonably sure that a therapy is safe. For this, registries and RWE capture needs to be developed along the way.

For EMA as a regulator, this requires flexibility in choosing between what is ‘must have’ and what is ‘nice to have’ information; a difficult balance to strike and one which we can improve. However, at the end of the day, our mandate is public health, which we must continue to pursue.

In your opinion, which actor (or actors) should be the custodians of this data? When we talk to clinicians, this question still seems somewhat ill-defined.

There is no single right way of collecting and storing such data. There are two major concerns: where the data is coming from in terms of both input and maintenance and who decides who uses it and for what. Both are extremely difficult to resolve.

EMA defines what it would like in a perfect world and then sees how close it can get to that. Ideally, such data would be stored in well-established public bodies, such as universities or hospitals, because companies – by their nature – go bankrupt, sell products, or merge with other firms. Given that we require 15 years of data, we want to be sure that the institution holding that data is still

around in 15 years' time.

Other challenges include compatibility; registries and databases are put in place by different people at different moments of history, meaning that it's difficult to communicate with each other. Moreover, keeping the data clean is very expensive, as is the task of following up with patients annually, the issue of consent, questions around intellectual property, and ensuring that the actors conducting RWE studies are doing them properly. If unfair top-line results are returned – as happened during COVID-19 – these can be very frightening and easily misinterpreted.

Therefore, we must always remember the importance of these data and be open to coming together in inter-stakeholder partnerships. Go-CART is such an initiative, but there are many others, and many registries from various countries are now trying to define the minimum data that is needed. Inputting and maintaining these data sets is very expensive and time consuming.

At EMA, we made a big step forward on this issue with the launch of the Data Analysis and Real-World Interrogation Network (DARWIN EU) which will deliver real-world evidence from across Europe on diseases, populations, and the uses and performance of medicines, enabling EMA and national competent authorities in the European medicines regulatory network to use these data whenever needed throughout the lifecycle of a medicinal product. However, there is always more that can be done.

Commercial companies have told us of their frustration that ATMPs are stuck as late lines of treatment and that they are unable to make the case for them to be used earlier. What is your view?

Whenever we at EMA receive a dossier, we judge the therapy based on the information contained within. The actors who make the decisions for first-in-human trials are the national level clinical trial authorisation bodies. However, as a doctor, I put myself in their shoes and understand that these are often quite revolutionary therapies that do not fit into the traditional treatment paradigm.

Nevertheless, almost all new treatments are first introduced in a reduced indication or as a fifth line treatment and then they move up the chain depending on how well they work. This has been the case with both immunotherapies and monoclonal antibodies, for example. It is natural that medicine developers want this process to move more quickly, but we must continue to take decisions based on available evidence. Another aspect to consider is that these are very expensive therapies, meaning that there is a need to start small and grow from there, rather than

immediately treating large groups of patients.

One of the ethical dilemmas you have voiced in the past, and which we have discussed with several clinicians and industry sponsors, is how to deal with out-of-specification (OOS) therapies, i.e., when an advanced therapy presents one or more parameters that fall outside the authorised specifications. Are country-led “hospital exemptions” a solution to this?

OOS therapies and hospital exemptions are very different things. OOS therapies are those where the product a doctor has in hand in front of their patient is not exactly what has been approved. If this is a basic medicine, such as aspirin, the medicine is disposed of, and another is used.

However, with advanced therapies, this is not possible. Often, these therapies are based on cells that came from the patient, have been genetically modified, and now a few weeks later, are ready to be put back into the patient. In some cases, these cells then fall outside of the parameters set by regulation – such as having a survival rate under the level stipulated in the marketing authorisation. The decision to administer that drug is with the clinician.. As regulators, we do not like this situation as it puts a lot of pressure on both the doctor involved and the patient if they are involved in the decision-making process, but we accept that these decisions sometimes need to be taken. OOS situations occur due to the complexity of these therapies and of their manufacturing processes, although the system is improving overall, as is manufacturing.

Hospital exemptions, on the other hand, are a very local way to authorise medicines and have a very important role to play in one-off treatments. An example might be a baby born with an essential part of its throat missing. This missing part can be grown locally in a lab using the baby’s own cells and then transplanted. For these one-off treatments, permission is sought on a national level.

These therapies by definition don’t travel outside of a particular hospital. But if enough experience and data are accumulated, they could be reproduced elsewhere and end up becoming a commercialised medicine. EMA recognises the importance of this pathway and has worked on taking several products developed in this manner and bringing them to Europe-wide use.

Of course, we would always like to see these treatments produced a lot closer to the patient – ideally in the same hospital – rather than flying them across the world. Many hospitals in Europe now have GMP-accredited facilities to do so, but it will take time to get to the final destination.

Some industry sponsors have even raised the issue that hospital exemptions may pose a threat to innovation and IP protection. Do you reject these accusations?

I would argue in the strongest possible terms that these exemptions are not a threat to innovation. Hospital exemptions are very heavily controlled by national competent authorities which make sure that all the GMPs are in place, it is not a free for all. If it was, there would be hundreds of hospital exemptions which is simply not the case.

Some medicines will always need to be produced in the types of large manufacturing facilities run by big pharmaceutical companies. However, for other medicines, there may be another way to go. We could see many smaller companies emerge, as we have seen in medtech, where 90 percent of firms are very small outfits that do one thing very well. Additionally, the medical space now includes a host of new entrants in fields ranging from IT to apps, devices, delivery systems, and companion diagnostics; showing that innovation is not limited to large companies with large factories; it is much more multifaceted. Regardless of whether it is local or global manufacturing, to produce ATMPs and indeed any medicines, standards must remain extremely high. This is a matter of public health with a lot at stake.

Is the increase in the number of contract manufacturers in what is still an experimental field a challenge or does it bring us closer to being able to manufacture advanced therapies at a sufficient scale?

This is a normal evolution in the development of new types of medicines. A case in point is the first biologicals and now the production of biosimilars. A few years ago, the industrialisation of these products may have seemed too difficult, but they are now being produced in industrial quantities; it is a question of time. However, biosimilars are cheaper to develop than originator medicines, but still not cheap, and ‘simplifying’ such complex biological products is never easy or quick.

During our previous discussion you mentioned the different approaches being taken by regulators and how for the EMA, the basic principle is to ensure that advanced therapies will be used by the patients, not merely made available on the market. Moving from a challenging present to a future full of promise, what do you see as the potential game-changers in terms of the adoption of these therapies?

This is a difficult question because it requires a fair amount of guesswork but, in essence, I am hoping for more translation. The pyramid is currently very unbalanced, with a huge amount of investment into basic science, especially at the public level, but only 17 or 18 ATMPs on the market. In another ten years' time, I would like to see this balance redressed. Moreover, I hope to see progress not only in the medicines themselves, but also in everything around them, from diagnostics to delivery systems. This will lead to a host of new market entrants and a wider stakeholder ecosystem.

Gene modification has been thrust into the headlines once more with some of the COVID-19 vaccines and is a topic that the public are somewhat apprehensive about. Are you any closer to establishing global collaborations and consensuses on the boundaries within this field?

The collaboration is there and is growing, precisely because the public is rightly fearful of these new technologies with potentially irreversible effects. Moving forward, we are not taking anything for granted and we are continuing to make data-driven decisions; balancing the potential benefits that gene modifying technology can bring with an appreciation of its dangers and drawbacks.

Do you have a final message for PharmaBoardroom's global audience?

This is a fantastic time to be involved with advanced therapies and I would encourage all students thinking of studying biotechnology to do so; this is the future and has so much to offer. However, biotechnology is very complex, meaning that it is not the sector for those seeking quick results. Nevertheless, we have built a very solid base from which to grow, and I am expecting great things in the next five to ten years.

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