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Article Pack

Regional Comparisons of Pharmaceutical Regulations

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Introduction

Our articles illuminating differences in performance and regulatory expectations for policy agencies in different markets set us apart from competitors. They compare regional drug review trends, approval decisions and regulatory guidance, often in context of how a specific drug or biotech product fared in different regions.

These insights reduce the complexity of navigating multiple markets and increase prospects for product marketing authorization.

Find these articles quickly at *Pink Sheet's* Regional Comparisons page on our website.

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Vibha Sharma

24 Jul 2023

Executive Summary

In this regional comparison, regulatory experts at a US-based decentralized clinical trials (DCT) firm discuss their views on how the FDA's draft DCT guideline compares with the pan-EU recommendation paper on this topic. This first segment of a two-part article dwells on the thinking behind why US and EU regulators tend to go down different paths.

Both US and EU regulators recognize the important potential benefits and value of decentralized clinical trials (DCTs) and are keen to support such studies. Their respective guidelines on DCTs – issued just five months apart – are largely similar but have some notable differences.

The US Food and Drug Administration published its draft DCT guideline in May, with stakeholder comments being accepted until 1 August. EU regulators offered their harmonized perspective on the use of decentralized elements in clinical trials in a final recommendation paper in December 2022.

DCTs allow some or all trial-related activities to be centered around participants, typically enhanced by health technologies. These trials gained prominence during the COVID-19 pandemic, when travel and social distancing-related restrictions made in-person clinical research visits difficult.

While the FDA guideline and the EU paper both underline the importance of ensuring that the use of any decentralized element in a trial should be "fit for purpose," they differ in their level of prescriptiveness, says Kevin Potgieter, vice-president of regulatory affairs at the US-based virtual clinical trials solutions provider Medable.

In its guideline, the FDA has made a purposeful choice to write in broad strokes, stopping short of detailing specific ways to execute decentralized or tech-enabled clinical trials.

This comes as no surprise to Potgieter, who explained that whenever the FDA deals with something new, it tends to allow more freedom and maneuverability, which enables businesses to advance innovation faster than they would have otherwise if the agency were very prescriptive. (Also see "Decentralized Clinical Trials Could Affect Validity Of Non-Inferiority Finding, US FDA Says" – Pink Sheet, 2 May, 2023.)

Kevin Potgieter is Vice-President of Regulatory Affairs at Medable

This is quite different to how things are done in the EU where, for example, when it comes to complying with new requirements such as those laid down in the Clinical Trials Regulation or the Medical Devices Regulation, "it's very much about 'Here's how you need to do it' and 'Here's the prescription that you have to follow'," noted Potgieter.

"It's a very different approach" between the two regions in terms of the "level of prescriptiveness that is expected" to demonstrate compliance with software requirements to support DCTs – Kevin Potgieter, Medable

This philosophical difference between the US and the EU becomes evident in their respective DCT recommendations, although "to a lesser degree," he said.

An example of a prescriptive requirement in the EU recommendation paper is that when it comes to using software to support DCTs, it now points to the recently-finalized European Medicines Agency guideline on the use of computerized systems and electronic data in clinical trials. This final guideline contains specific considerations for software development, testing and functional requirements. (Also see "EMA Finalizes Key Guideline On Use Of Digital Tech To Capture Electronic Trial Data" – Pink Sheet, 14 Mar, 2023.)

By contrast, in the US the FDA points to the new draft guidance on Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations, which in turn points to the overarching Part 11 of the Code of Federal Regulation (ie, the FDA's regulation for electronic documentation and electronic signatures).

"It's a very different approach" between the two regions in terms of the "level of prescriptiveness that is expected" to demonstrate compliance with software requirements for electronic informed consent, electronic patient-reported outcomes(ePRO)/ electronic clinical outcome assessment(eCOA) and other DCT elements, Potgieter said.

Principles-Based vs Prescriptive: How US & EU Compare In Their Approach To Decentralized Trials

Pamela Tenaerts is Chief Scientific Officer at Medable

As global technology solution providers have to meet the "higher bar" when designing their software, they follow the EU requirements which point to very specific deliverables. These "more than satisfy the US requirement," but "we don't see that explicit requirement in the US side," Potgieter explained.

Another example of a prescriptive requirement in the EU recommendation paper is its emphasis on a physical, in-person meeting between the potential trial participant and the study investigator during the informed consent process, although it permits this to be done remotely in certain circumstances, said Pamela Tenaerts, chief scientific officer at Medable.

In the paper, EU regulators also explain why a physical meeting may be more necessary for some trials, for example those involving vulnerable populations, and "almost start directing or giving an indication of how people should think about it," Tenaerts noted.

The EU DCT recommendation paper places greater emphasis on aspects like quality by design – Pamela Tenaerts, Medable.

The FDA's guideline is more of a "principles-based" document that encourages stakeholders to think about "what's right for the circumstance of the trial, of the participant" and of the technology being used, she added.

In contrast, the EU paper places greater emphasis on aspects like quality by design and focusing on critical-to-quality factors with respect to the trial's design and giving importance to the patient's voice in designing the DCT, Tenaerts noted. Moreover, given that all 30 member states in the European Economic

DCT Regional Comparison

This article is part of a Pink Sheet analysis of DCT regulation in the EU and US.

- Another articles looks at how the EU and the US compare on the more practical aspects of running DCTs, such as presenting information on decentralized elements in trial dossiers, dealing with the sponsor-investigator overlap, and the use of local health care providers. (Also see "Different, But Not Poles Apart: Running Decentralized Clinical Trials In EU & US" – Pink Sheet, 25 Jul, 2023.)
- A companion article to the one provided here a deeper dive into some aspects of the US draft guidance. (Also see "FDA's Decentralized Trial Guidance: Investigator, Health Care Provider Demarcation Raises Questions" – Pink Sheet, 24 Jul, 2023.)

Area have a voice, "you see that come out in some of this." (Also see "EU Aims To Drive Uptake In Decentralized Clinical Trials With Harmonized Guide" – Pink Sheet, 15 Dec, 2022.)

As such, Tenaerts believes that guidance documents should not be too specific as they can get "outdated pretty quickly," as was the case with International Council for Harmonization's first guideline on good clinical practice requirements (E6) issued in 1996. That happened because "back then, they didn't think about electronic systems" or "any of those things," she noted.

The principles-based approach, Tenaerts explained, encourages people to "think about what you're trying to do and do the right thing" and this has its benefits because "who knows what the next thing is that we're going to be using in clinical trials." She noted that guidances are meant to work for all kinds of situations and "if you get very specific, you kind of back yourself in a corner."

Potgieter does not expect the US guideline to remain a high-level document for long. "I guarantee, over the years there will be course correction" when issues crop up that are essentially the equivalent of a safety or a data integrity signal, he said. The FDA will find that "sponsors struggle with this thing, so we need to provide a little bit more [guidance]."

The EU regulators too have indicated that the DCT recommendation paper would evolve continuously given the "rapid advances" in the field of DCTs. The current focus, however, is on reviewing and tracking DCTs to gain experience before considering the need for any updates to the paper. (Also see "EU Countries Focus On National Best Practices For Decentralized Trial Approvals & Inspections" – Pink Sheet, 23 Jun, 2023.)

Interplay Of Other Guidances

For sponsors planning to undertake DCTs in the EU or the US, the Medable executives said they must also look at other documents and legislation in these regions that may affect the deployment of decentralized elements.

In the US, for example, there are a series of guidelines on patient-focused drug development as well as recommendations on electronic informed consent (eConsent). Likewise in the EU, additional aspects to consider include the General Data Protection Regulation and the EU digital signature legislation.

Another major document that will impact DCTs globally is the ICH E6(R3) draft guideline, which has been updated to explain how GCP principles can be applied to emerging innovations in trial design and conduct. (Also see "ICH Consults On Modernized GCP Principles To Make Clinical Trials More Efficient" – Pink Sheet, 25 May, 2023.)

Tenaerts believes that the draft E6(R3) includes elements that are closer to the EU DCT recommendation paper, which is relatively more prescriptive. "It will be very interesting to see, as the harmonization period for ICH E6(R3) comes up, how much … within the FDA guidance will shift" because the ICH guideline at present is "more EU in spirit", said Potgieter.

While the ICH harmonization process is expected to take a long time (the draft E6(R3) was only issued for stakeholder consultation in May 2023), Potgieter said "where the rubber meets the road most" will be when sponsors start submitting applications for investigational new drugs proposing new studies that include up to seven to eight different DCT elements and seeing how the FDA provides feedback. For example, whether it "gives them a thumbs up or thumbs down, or says, 'Hey, we need to see more on this element. How do you control that or mitigate the risk for this, etc'."

EMA And FDA Compared – The Case Of Minoryx's Leriglitazone

Francesca Bruce

06 Jul 2023

Executive Summary

The EMA offers more flexibility than the US FDA when it comes to missed primary endpoints in certain circumstances, meaning a potentially quicker route to authorization in the EU.

Spanish biotech firm Minoryx Therapeutics hopes a newly approved Phase III trial will lead to the US approval of its orphan drug leriglitazone for X-linked adrenoleukodystrophy (X-ALD) in 2026 at the earliest.

Meanwhile, the European Medicine Agency's review of the drug is well under way, with a decision on marketing authorization expected at the end of 2023 or the beginning of 2024. The *Pink Sheet* took a look at the different approaches to approval in the two markets and how missed primary endpoints and a lack of natural history data have impacted the route to authorization.

In June, the FDA gave Minoryx the go-ahead to initiate the Phase III CALYX trial of leriglitazone for treating X-ALD patients with cerebral adrenoleukodystrophy (cALD). The study is intended to lead to full approval in 2026, although the timeline could be longer. If the first efficacy readout for the study at 18 months does not show efficacy, there will be a second readout at a later date, followed by a third if necessary.

Key Takeaways

- The EMA offers a more flexible approach than the FDA when primary endpoints are missed for orphan products where there has been little natural history data of the disease to inform trial design.
- The review of leriglitazone is more advanced in Europe than in the US.
- Leriglitazone could be offered a conditional marketing authorization in the EU.

By contrast, in the EU, a review of the company's marketing authorization application by the EMA's committee for human medicinal products (CHMP) began in September 2022. The process is ongoing and the company is waiting for the next round of comments from the committee, said Marc Martinell, CEO of Minoryx, in an interview with the *Pink Sheet*. He expects an EU decision on authorization at the end of 2023, or the beginning of 2024 if the CHMP has any "unforeseen requirements". CALYX will have little bearing on the decision as the EU submission is based on the results of an earlier trial.

Endpoints

"There have always been some important differences in the development on both sides of the Atlantic and in the way the FDA and EMA have seen the product and what they have been requesting," said Martinell.

One notable difference has been the EMA's flexibility with regard to missed primary endpoints for a treatment for a rare disease with little natural history data available to inform trial design.

"When you move into the zone of results with a missed primary endpoint, that is when the differences between regulators become more pronounced… In Europe you may have more of a global picture perspective… whereas in the US, you are more tied by the primary endpoints," Martinell commented.

In the EU, the marketing authorization application for leriglitazone is based on the Phase II/III ADVANCE trial, a two-year double blind placebo controlled study that aimed to evaluate the efficacy of leriglitazone on the progression of adrenomyeloneuropathy (AMN) in male patients, determined by a motor function test. The study missed its primary endpoint in the overall population, which was a change from baseline in the 6-minute walk test.

The Disease

X-ALD is an orphan neurodegenerative disease with a global incidence of approximately 6.2/100,000 live births and which is characterized by demyelinating brain lesions. The lesions rapidly progress and lead to acute neurological decline and death. They also produce severe symptoms, including loss of voluntary movements, inability to swallow, loss of communication, cortical blindness and total incontinence and death, with a mean survival of three to four years.

Adrenomyeloneuropathy (AMN) and cerebral adrenoleukodystrophy (cALD) are the most common phenotypes. AMN, the chronic form of the disease, affects patients at adulthood and is characterized by progressive spastic paraparesis, sensory dysfunction and incontinence. AMN patients are also at risk of developing progressive cerebral lesions. cALD mostly affects males, and onset is typically between the age of four and eight. If untreated cALD progresses quickly and leads to permanent disability and death within two to four years.

Despite missing the primary endpoint, the study did yield "important results in other endpoints," said Martinell. It showed that leriglitazone reduced the progression of cerebral lesions and incidence of cALD and the progression of myelopathy symptoms, including balance deterioration.

"The reason why we missed the primary endpoint was essentially because of the lack of the proper understanding of the natural history of this disease," Martinell observed. "When we were starting, very little was known about X-ALD

and particularly AMN, the chronic component of the disease affecting the spinal cord. This was the target population under the study."

"The EMA recognized this sometime ago when we were discussing the study design," he said, adding that there were discussions on how to present the data in a pre-submission meeting.

Now there is more natural history data available and a better understanding about the disease progression. "There is a phase of disease when patients progress a lot on that endpoint and a phase where they do not," Martinell noted. Analysis of patients in the early phase of the disease versus those in later stage disease showed that there is an important effect on the early stage group with regard to the primary endpoint. According to Martinell, the company has been able to set this out to the EMA. "This is the kind of consideration we describe in the file."

Meanwhile, in the US the company had anticipated that another trial would be necessary. The FDA wanted a larger sample size of patients and a study with primary endpoints that definitively showed clinical benefit, said Martinell. The FDA-approved CALYX Phase III trial is designed to satisfy these requests and is enrolling 40 male X-ALD patients with progressive cALD defined by the presence of gadolinium-enhancing brain lesions. The primary endpoint of the placebo controlled trial is time to death or bedridden with permanent ventilatory support.

CMA vs Accelerated Approval

Another important difference between the two regulatory systems is that in the EU there is the possibility of receiving conditional marketing authorization (CMA). "You don't have the equivalent in the US. You have accelerated approval. That can change things and be why you may end up in different situations on both sides [of the Atlantic]."

In the EU products are eligible for a CMA if they are intended to treat or prevent a seriously debilitating or life threatening disease. They must serve an unmet need and have a positive benefit-risk profile. When a CMA has been granted, the authorization holder must fulfill certain obligations, such as completing ongoing studies, starting new studies or collecting additional data to confirm the medicine's positive benefit-risk profile. Martinell did not rule out the possibility of a conditional marketing authorization for leriglitazone in the EU.

In the US, the accelerated approval pathway allows for earlier authorization of drugs that fulfill an unmet need and treat serious conditions based on a surrogate endpoint. Companies are then expected to conduct further studies to confirm the expected clinical benefit.

CALYX is intended to lead to full approval straightaway as the primary endpoint is on survival, said Martinell, though he acknowledged the accelerated approval pathway could be a possibility if primary endpoints are not hit.

PIP

A third difference between the two markets is the requirement that in the EU the company must produce a pediatric investigation plan (PIP) detailing clinical studies to be conducted in children, unless a waiver is granted.

As part of its EMA-approved PIP, Minoryx is conducting the NEXUS study in 20 boys between two and 12 years old with cALD with brain lesions with or without gadolinium enhancement. The primary endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96. Interim results included in the EU filing for leriglitazone show that all evaluable patients were clinically stable with radiologically demonstrated disease arrest or lesion growth stabilization after 24 weeks.

How Do Japan's Clinical Trial eConsent Rules Compare With The EU And US?

Eliza Slawther
10 Aug 2023

Executive Summary

A newly translated guidance document from Japan's drug and device regulator outlines the points that clinical trial sponsors should consider when using electronic methods to collect informed consent from participants.

Sponsors of clinical trials in Japan can use electronic methods to explain and obtain informed consent from participants (eConsent), as long as communication is provided "at the same level as a conventional face-to-face setting," according to guidance from the Pharmaceuticals and Medical Devices Agency.

In a document that was translated into English this month following the March publication of the original Japanese language version, the PMDA outlines considerations for companies that are looking to use eConsent in the clinical trial process.

The PMDA notes in its guidance that the uptake of eConsent technology has improved the efficiency of clinical trials. Although it highlights some circumstances where using more traditional, physical methods of explaining and obtaining trial participant consent might be appropriate, the guidance broadly supports the use of digital tools during this process.

eConsent refers to using remote communication mechanisms such as digital documents or video calls to provide potential clinical trial participants with the information they need to make a decision on whether to participate in the study, and to collect their consent, for instance through the use of electronic signatures.

Japan's guidance is similar to the approach taken by the US Food and Drug Administration,

which encourages sponsors to consider the individual circumstances of a trial and the participant during the consent process. (Also see "Principles-Based vs Prescriptive: How US & EU Compare In Their Approach To Decentralized Trials" – Pink Sheet, 24 Jul, 2023.).

By contrast, EU guidelines on using electronic tools during clinical trials emphasize the importance of conducting physical meetings where possible during the consent process, but say that eConsent methods are permitted "where this can be justified and is allowed nationally and if approved by an ethics committee."

The production of a global database that describes country-level requirements for eConsent is one key aim of an ongoing EU initiative launched to boost the uptake of this technology in Europe, where its use is currently limited.

The project, run by the EU Forum for Good Clinical Practice, also aims to address challenges such as a lack of harmonization around eConsent terminologies and unclear regulatory, ethics and privacy requirements (Also see "EU Multistakeholder Project Aims To Give eConsent The 'Place It Deserves'" – Pink Sheet, 6 Jun, 2023.).

Sponsors conducting clinical trials in Japan should evaluate the "appropriateness" of using eConsent methods during the clinical trial design process and put forward an eConsent procedure for review by the institutional review board, the PMDA says, although the document does not state that sponsors must justify the decision to use eConsent instead of physical meetings.

There are some cases where sponsors must consider whether eConsent is suitable, the PMDA notes, such as where participants are unable or unwilling to use digital consent tools. Face-to-face meetings should be offered as an alternative in these situations.

Sponsors also need to account for individual variations in digital literacy or accessibility when setting up eConsent IT systems, and ensure that participants are offered training or additional information so they can operate systems appropriately.

The PMDA document also provides information and advice around verifying participants' identities, the use of video and phone calls, requirements for electronic signatures, and the secure storage of eConsent records.

Gene Therapy HTA: How Do The European, Australian And Canadian Systems Shape Up?

Eliza Slawther

25 Sep 2023

Executive Summary

A report comparing the health technology assessment methods used in nine European countries, Australia and Canada found that England has the most favorable reimbursement landscape for gene therapies – but outlined several areas for improvement across the board.

There are six main actions that health technology assessment organizations should implement to capture the value of gene therapies, according to researchers from the UK's Office for Health Economics (OHE). Yet, the organization suggested in a recent report, wide variations in the HTA methods used within different countries demonstrate the importance of continued changes to HTA methodologies and evidence generation to enable the potential benefits of gene therapies to be realized.

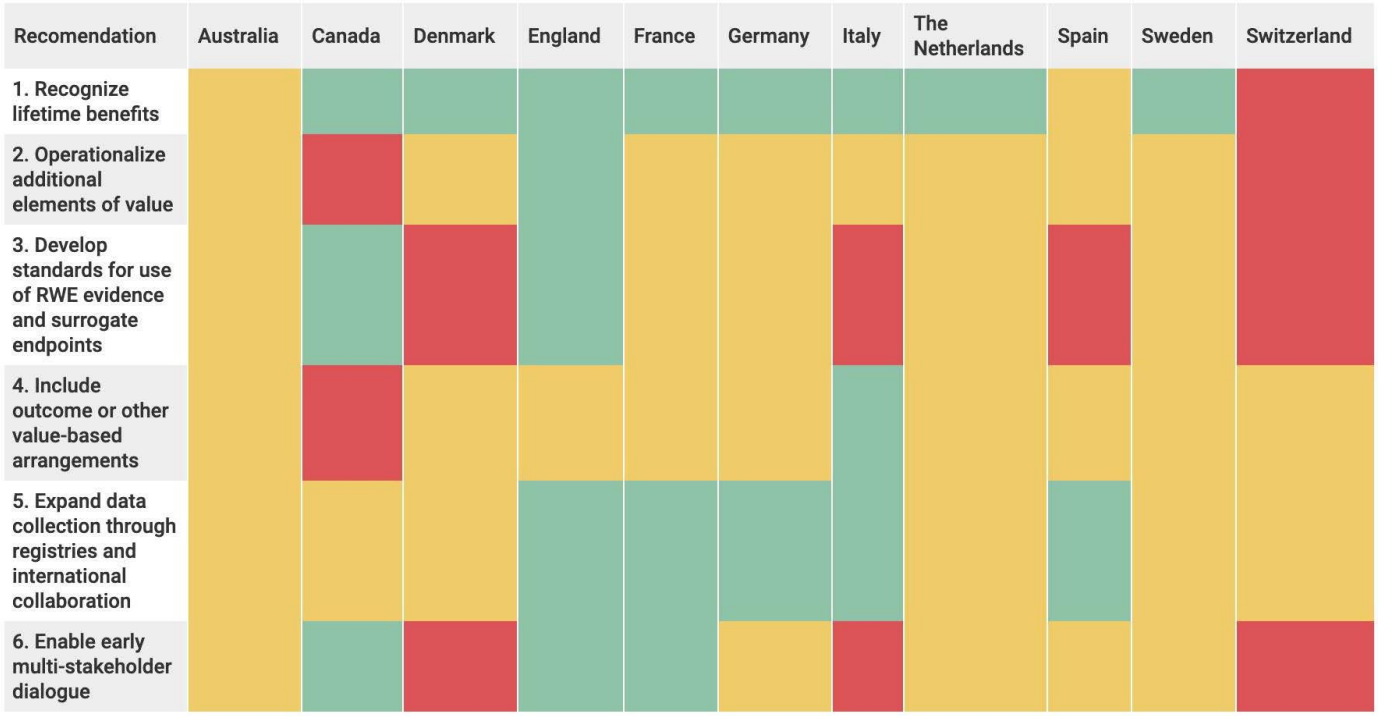
Some of its recommended actions include the development of standards for the use of real-world evidence and surrogate endpoints in HTAs, the inclusion of patient-reported outcomes and the use of data collected in international registries.

In a report published earlier this month, the OHE compared the extent to which 11 different countries have achieved these actions, and found that England was the highest performer, having implemented five out of the six recommended. Switzerland, on the opposite end of the scale, appeared to have carried out the fewest number of actions recommended by the researchers (*see table*).

Comparison Of Gene Therapy HTA Across Countries

Data from the OHE, 2023 on the degree to which 11 countries' HTA systems met each of its recommended priority actions.

Besley S., Henderson N., Napier., M., Cole., A., Hampson G., 2023. Country Scorecards: Health Technology Assessment of Gene Therapies. OHE Consulting Report, London: Office of Health Economics.



Green = recommendation achieved
Yellow = recommendation partly achieved
Red = recommendation not achieved

England's HTA body, NICE, was found to have fully achieved all but one of these recommended actions. The only one it had not met was the inclusion of outcome or other value-based arrangement in its methods, which the report said NICE "partly achieved".

The countries included in the report were Australia, Canada, Denmark, France, England, Germany, Italy, the Netherlands, Spain, Sweden and Switzerland. The report looked at how well, if at all, the HTA organization for each country met each of the six recommendations, and considered the reimbursement status of nine gene therapies.

Sian Besley, lead author of the report and an economist at the OHE, told the *Pink Sheet* that many additional value elements from what's known as Lakdawalla's value flower "are not considered in current HTA methods". Also known as the International Society for

Pharmacoeconomics and Outcomes Research (ISPOR) value flower, this model includes 12 potentially underappreciated or ignored elements of value in conventional drug HTAs such as equity, disease severity, and adherence-improving factors.

For example, she said "the value of hope – which may be very relevant for many gene therapies" – is not always considered.

However, Besley explained that the key takeaway from the report is that for the fourth recommendation, which related to capturing benefits beyond the clinical efficacy of a medicine, "value elements are often not consistently and transparently considered across technologies."

Italy's Agenzia Italiana del Farmaco (AIFA), which is the country's medicines regulator as well as its pricing and HTA authority, was the only one found to fully achieve the fourth recommendation – "many outcomes-based and economic risk-sharing agreements have been implemented, making use of their well-established registries," the report said.

In Italy, staged payments linked to individual patient outcomes were in place for two gene therapies, but the report noted that there had been a recent decline in the use of outcome-based payments in Italy "in favor of confidential price discounts."

"The recommendations are not specific to the HTA of gene therapies and should be consistently applied across HTA of other treatments," the report said. "However, due to the combination of challenges presented by the HTA of gene therapies, if implemented, the recommendations are likely to have a larger impact on the assessment of gene therapies."

There has been a growing consensus in recent years that traditional HTA methods are suited more towards chronic therapies, rather than novel gene therapies that are intended to be a cure, or at least provide long-term symptomatic relief for individuals with genetic diseases. (Also see "Advanced Therapies: Payment Revolution Must Accompany Industrial Revolution In Europe" – Pink Sheet, 12 Aug, 2022.).

Often, these therapies come with price tags that far exceed $1m per patient. CSL Behring's hemophilia B gene therapy Hemgenix (etranacogene dezaparvovec), for example, has a list price of $3.5m, and was recently provisionally turned down for reimbursement in England, although negotiations are ongoing. (Also see "England: CSL Undeterred By Draft NICE Rejection Of Its £2.6m Hemophilia B Gene Therapy" – Pink Sheet, 2 Aug, 2023.).

Country Comparisons

Most of the countries included in the report achieved the first recommendation of using HTA methods that recognize the lifetime benefits offered by a therapy. However, Australia and Spain only partially achieved this metric, while Switzerland did not achieve it at all.

Switzerland scored lowest overall in terms of meeting the six recommendations. It did not fully achieve any of them, and only partially achieved two, which were including outcome or other value-based arrangements and expanding data collection through registries and international collaboration.

Besley explained that the large variations between HTA bodies were "not surprising" given that some were more established than others. "The key benefit of our analysis lies in uncovering where these variations may impact the HTA of gene therapies," she said.

"Many of our recommendations focus on ensuring that methods to improve the appropriateness of HTA for gene therapies are clear and transparently implemented. This is

not always the case, and efforts are needed to embed the principles explicitly into published national HTA methods and guidelines," she continued.

Further research is also needed to assess the barriers that are preventing countries from implementing the OHE recommendations, Besley said, which would then be followed by an exploration of how these barriers could be overcome.

NICE Moving To 'Modular Approach'

The report reflected favorably on England's NICE, and praised its highly specialized technologies (HSTs) program, which it said was an example of extra value being recognized for very rare technologies beyond the number of quality-adjusted life years (QALYs) gained.

"The HST pathway offers a more pragmatic approach to dealing with uncertainty," the OHE report said. NICE's real-world evidence framework was also found to be "the most comprehensive guideline for the inclusion of RWE in HTA."

A spokesperson for NICE said that the HTA body recognized the high potential and transformative health benefits of innovative technologies such as gene therapies, "and the importance of robust health technology assessments to secure rapid, evidence-based patient access and value for money."

"It's great to see the OHE recognize NICE's assessments are based on processes and methods that are fit-for-purpose even when addressing these more complex treatments," the spokesperson said.

"NICE will ensure its manual remains cutting edge by moving to a modular approach for any future updates, allowing us to update our processes and methods in an agile and responsive way," the spokesperson added.

Orchard Therapeutics, the manufacturer of Libmeldy (atidarsagene autotemcel), an ex-vivo gene therapy used to treat children with metachromatic leukodystrophy, told the Pink Sheet that the patient perspective had been incorporated into the NICE HTA process in its experience.

"That's really important in terms of being able to fill in some of the evidence gaps, which you cannot inform [just] by using [trial] data," Francis Pang, senior vice president for global market access at Orchard, told the *Pink Sheet* in a recent interview.

Libmeldy was reimbursed in England in February 2022, after a new pricing agreement was reached following an initial rejection from NICE. (Also see "Libmeldy: 'Significant Discount' For World's Most Expensive Drug Secures English Funding" – Pink Sheet, 4 Feb, 2022.).

During the interview, which will be published in full later this month, Pang also discussed the access challenges involved in getting innovative, advanced therapy medicinal products (ATMPs) such as Libmeldy to patients across the globe, and explained how HTA processes can be adapted to meet the needs of gene therapies.

EU Joint HTA Impact

The upcoming EU-wide joint clinical assessments (JCAs) introduced by the EU regulation on HTA could see some of the variations in the methods used by EU member states to assess gene therapies removed, given that JCAs will be conducted at an EU level rather than nationally. The outcomes of JCAs will not, however, be legally binding for national reimbursement and pricing decisions.

Paolo Morgese, head of public affairs, Europe, at the Alliance For Regenerative Medicine (ARM), told the *Pink Sheet* that the OHE report "draws conclusions similar to recent ARM research."

"While at varying degrees, several national HTA bodies are adapting their methodologies to fit the unique nature of ATMPs," he said, adding that the pan-European JCAs due to take effect in 2025 "should be inspired by HTA modernization in countries like the UK, Germany, France, Italy, and Sweden."

The ARM has previously discussed its concerns about the upcoming joint HTA assessments, although it has broadly supported the legislation in principle given the potential for EU-level JCAs to reduce the administrative burden on companies seeking reimbursement for advanced therapies. (Also see "Direction Of Travel Of EU HTA Regulation Is 'Disappointing' For Advanced Therapies" – Pink Sheet, 6 Dec, 2022.).

HTA bodies are not the only organizations that have struggled in recent years to assess the value of gene therapies. Regulators across the globe also face ongoing challenges in deciding whether a gene therapy is likely to be beneficial in the long term, given that the data are not available until patients treated with gene therapies have lived for many years. (Also see "Gene Therapy: Years After Accelerated Approval, Will US FDA Still Be Asking 'Does It Work?'" – Pink Sheet, 20 Feb, 2023.).

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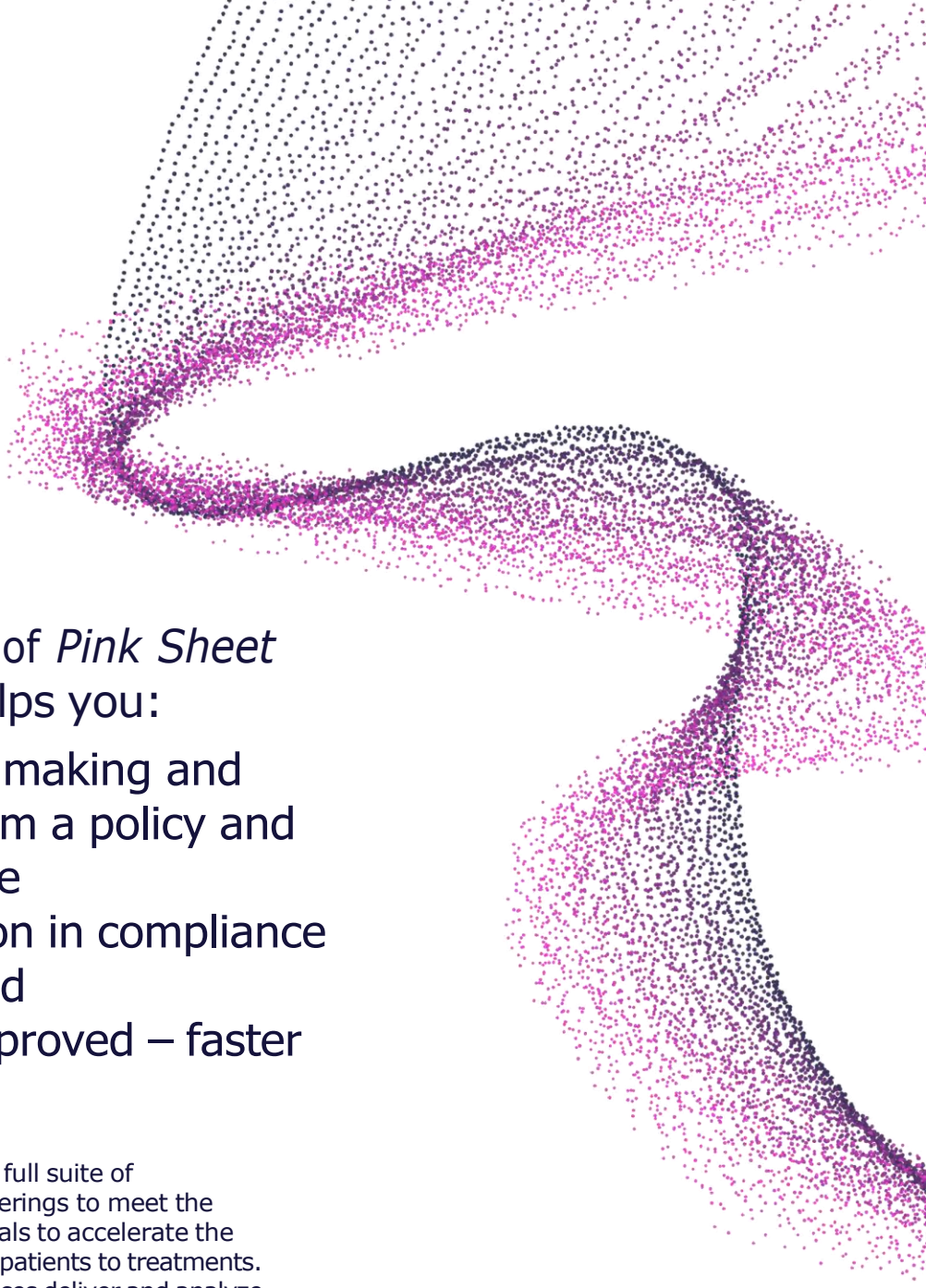

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