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FDA-EMA Advice Pilot For Complex Generics: What Does Industry Have To Say?

Voices From Medicines For Europe, Association For Accessible Medicines And Sandoz

by Urtė Fultinavičiūtė

The FDA and EMA have shared perspectives on the parallel scientific advice pilot for complex generics. Now industry stakeholders discuss whether transatlantic convergence is possible or merely a good idea on paper.

Scientific convergence between the US Food and Drug Administration and the European Medicines Agency has been ongoing for several decades. First, it started with programs for new drugs, then both agencies set up a cluster to discuss topics of mutual interest on biosimilars, an off-patent version of a biologic product.

However, complex generics, or hybrid medicines in Europe, had not been part of the transatlantic discussion, said Beata Stepniewska, head of regulatory affairs at off-patent association Medicines for Europe. She told *In Vivo* that the complex generics sector was “a bit of an empty space” and the industry needed a platform to have harmonization or convergence discussions.

In September 2021, the FDA and EMA launched a parallel scientific advice pilot to jointly exchange their views on scientific development questions with applicants.

Still, the pilot has not found its place in the industry. Since its launch, only two applicants have been granted PSA meetings and have completed the process. The FDA said that while certain misconceptions might be a reason for slow uptake, the agency assured that those “concerns may be unfounded.” (Also see "*FDA-EMA Pilot Advice Scheme On Complex Generics Sees Slow Uptake*" - Generics Bulletin, 12 Feb, 2024.).

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Unknown Territory That Has A Potential

At the end of February, the FDA hosted a webinar, titled "Expanding Generic Drug Access Through International Engagements," during which representatives from both agencies discussed the progress so far and debated factors that may limit the industry's participation in the pilot.

Indeed, what is missing in this conversation is the voice of the industry. It might be the case that because the pilot is still young, with a limited number of participants completing the process, it is difficult to have clear observations.

"You're on the beginning curve of this," David Gaugh, interim president and CEO at US off-patent group Association for Accessible Medicines, told *In Vivo* when asked about what the overall feeling towards the pilot is so far.

"You're getting in very early, which is good, but you're going to find that we won't have concrete answers for some of the questions you're going to have just because it hasn't developed far enough yet," he added.

Canada Considers Joining FDA-EMA Complex Generic Advice Scheme, But Is It Working?

By Urtė Fultinavičiūtė

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Health Canada is open to the collaborative effort but is still in "preliminary discussions," while the FDA and EMA try to attract more applicants to the parallel scientific advice pilot scheme for complex generics.

Read the full article here

AAM's senior vice president of sciences and regulatory affairs Giuseppe Randazzo seconded this, saying that the overall feeling is still a little bit unknown. While the PSA pilot could be a tool that could lead to increased harmonization, "there haven't been enough participants to help spread the word," Randazzo noted.

Pathways, Timings, Patents And Capacity

Despite being a step in the right direction leading towards a more global regulatory network, the pilot had its limitations, said Michael Banks, head of regulatory at *Sandoz*, one of the biggest companies in the generics and biosimilars industry.

One of the limitations is the differences in filing procedures in the US and Europe. For example, the PSA pilot is available for applicants who will go through EMA's centralized procedure, meaning the approval is coordinated by EMA directly and leads to a pan-European license.

However, most generic drugs are authorized via decentralized or mutual recognition procedures, when one Member State takes the lead in the scientific assessment on behalf of other member

states involved. The decentralized procedure is often a lot less expensive, given that fewer countries are involved, and generics in the centralized procedure are also limited by which originator products were approved in the same way.

Another hurdle is the timing of filing. Randazzo explained that some companies have research and development at different stages in the US and Europe. “Part of this is past practice, part of that is they know the logistical scheme in doing so,” he said, adding that differences in review or assessment process make it nearly impossible to align the submission and approval dates.

Patents and exclusivity are also factors that may influence submission in both regions. For instance, the initial data exclusivity in one region expires a lot earlier than it does in the other – in the US, it is as early as four years, whereas in Europe, it is eight years at the moment. “Depending on the patent timing, you could, in theory, be at the end of your review in the US, or even approved, before the data exclusivity expires in Europe,” said Banks.

It also all boils down to the company’s capacity and size. “You have the Tevas and Sandozs of the world and many large Indian companies that are multi-regional, but many of the smaller companies are not. So, they really wouldn't care that this process is moving forward because they're only going to be in Europe or the US,” said Gaugh.

Also, generic developers may not have the ability to launch products simultaneously with two major regulators. As Randazzo puts it, “sometimes some smaller companies will need approval and marketing in one health authority to bring some money in before being able to move on to the next health authority.”

Limitations Of Legal Text

Another key factor that may make participation in this pilot more challenging is the acceptance of a single comparator, said Stepniewska. While everyone is trying to find solutions on how to avoid the repetition of studies for the originator's product, the generics industry does not receive the same attention.

She clarified that despite reaching a mutual agreement between the applicant and regulators on the studies for approval, the clinical program must still be conducted twice due to the lack of acceptance of a single comparator. As Kevin Blake, EMA’s senior scientific specialist of clinical pharmacology, emphasized during the FDA’s February webinar, the use of an EU reference product is non-negotiable. He stressed that the Parallel Scientific Advice program should not be viewed as a platform for discussing the utilization of non-EU reference products.

Stepniewska said there was well-documented evidence showing that some reference products or comparators come from the same production for the EU and the US, simply highlighting the frustration of the generics industry. “It's an identical product, but still, because of this legal

interpretation, we are stuck. That's the major barrier," she noted.

Legal definitions of what is a complex generic or a hybrid product may also be a barrier. As Stepniewska describes it, a "hybrid is a bit unfortunate basket of everything that is between originators and generics." In Europe, if bioequivalence studies are not sufficient or appropriate, the product is deemed a hybrid because additional trials are required for approval.

"It is not only confusing for us, but it's also somehow recognized by the regulators that this definition or distinction doesn't fully reflect the nature of products," she explained, adding that definitions could be a barrier to participation, especially if the regulators are using them stringently as a criterion for selecting participants.

> ***Don't hide yourself behind the legal text. And if the legal text is unclear, change it.***

A solution to this issue? "Don't focus on the legal basis. Focus on issues to be solved, on science and a rational design of studies that are needed for this type of product," Stepniewska advised regulators.

What if the legal text is a limiting factor? "Don't hide yourself behind the legal text. And if the legal text is unclear, change it. Now it's the review of pharma legislation, that's a unique opportunity. So, change it, if you believe that it's needed," she added.

What's Next?

Both regulators and the industry are stuck in limbo – too few participants to draw conclusions about the pilot, too few examples to show it is worth participating. "It is a chicken and egg situation," joked Randazzo.

Certain incentives may make the pilot more attractive to the industry, such as waiving some of the fees. On the EU side, applicants still have to pay a fee for the meeting, so potentially removing the pre-submission meeting charge may be a way to incentivize the industry.

However, Stepniewska argued that reducing fees will not make huge progress. Instead, the focus should be on the single development concept. “There is no strong incentive to go for it. It's like two legs - we need a leg on the scientific advice, but we also need a leg on the practical execution of studies. While we don't have the second leg, we're not going to run,” she explained.

Indeed, if people could see a commitment from both agencies to meet in the middle, then there would be stronger uptake, said Banks. “It's a great initiative, but a lot of commitment is needed from both regulators for the industry to use it more,” he added.

Randazzo suggested that companies ask themselves early in the development process if it makes sense to pursue this pilot from a business perspective. No matter what the answer may be, simply “asking that question will be a good step for the industry and likely help the FDA or EMA in this pilot process,” he said.