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Biosimilars Council Urges Global Comparators And Dropping 'Unnecessary' Studies

US Industry Association Calls For 'Streamlining' Of FDA Approval Process For Biosimilars

by David Wallace

In a position paper published by the AAM's Biosimilars Council, the industry association has called for a streamlining of the FDA's approval process for biosimilars that includes eliminating "unnecessary" clinical efficacy studies and establishing global regulatory comparators.

The US Food and Drug Administration's biosimilar registration pathway should be streamlined by eliminating "unnecessary" clinical efficacy studies and establishing global regulatory comparators, according to a new position paper published by the Association for Accessible Medicines' Biosimilars Council.

Underlining that "around 80% of biologics currently do not have a biosimilar product in the works" – with around half of originator biologics facing loss of exclusivity within the next 10 years having no biosimilars in development – Biosimilars Council executive director Craig Burton said "let's reduce that percentage and pave the way for a new generation of lower-cost medications."

Bringing a biosimilar product to market is estimated to cost $100m-$300m, according to the *position paper*, with clinical efficacy studies typically accounting for half of research and development costs. The Biosimilars Council's suggested changes "would allow for the elimination of unnecessary regulatory requirements when data demonstrates no clinical meaningful difference between the biosimilar and its biologic reference product."

“Unnecessary clinical efficacy studies demand critical resources, delay competition and deter investment in lower cost biologic alternatives without improving the quality, safety, or efficacy of the treatments ultimately approved,” the paper argues. “Furthermore, this high expense reduces the number of biosimilars any given company can develop, leaving many originator biologics to dominate the market with no competition.”

The Biosimilars Council also emphasized that it is not seeking to eliminate clinical efficacy studies altogether, pointing to “the FDA’s authority to request additional evidence in exceptional circumstances where scientifically-justified, risk-based considerations are evident.”

> *“The time is now to update and streamline the current regulatory model for biosimilars.”*

Meanwhile, “unnecessary, duplicative PK testing of multiple reference products to support the requirements of various health authorities also contributes to the high cost of developing a biosimilar,” the paper states in support of its argument in favor of global comparators.

This means that “many patients in the US and globally will continue to be deprived of access to modern biologics because of high development costs unless the regulatory paradigm for developing biosimilar medicines changes, and development costs are reduced through the elimination of unnecessary comparative clinical efficacy studies and the establishment of global comparators for PK studies.”

With the development of new biological treatments for serious diseases “expanding rapidly,” the paper contends that “under the current regulatory framework, development of biosimilars for newly approved biologic medicines will be very costly.”

“The time is now to update and streamline the current regulatory model for biosimilars,” insisted Burton.

The call echoes comments made to *Generics Bulletin* earlier this year by AAM chair Keren Haruvi, who underlined the need to reduce the clinical trial burden for biosimilar sponsors. “You want to have competition in biosimilars, not just for the blockbuster,” she argued. (Also see "*‘Is The Market Now Sustainable? The Answer Is Still Not’: AAM’s Haruvi On The Need To Fix The US Generics Industry*" - Generics Bulletin, 13 Feb, 2024.)

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Advances In Analytical Methods Have Changed The Landscape

The two suggested changes are outlined in detail by the Biosimilars Council in its position paper.

Under the first – to "eliminate unnecessary clinical efficacy studies" – the paper requests that "to reduce the costs and risks of biosimilar development and encourage industry investment in biosimilars, FDA should clarify in regulations and/or guidance that requests for clinical efficacy studies should be the exception rather than a generally applied rule and explain the limited circumstances in which they might be scientifically justified."

"FDA should discourage the conduct of comparative efficacy studies when analytical, functional, and PK methodologies are sufficient to detect clinically meaningful differences," the paper suggests.

> *"In most cases, additional comparative clinical efficacy studies offer no meaningful, new, or actionable information."*

Setting out its rationale, the Biosimilars Council argues that "analytical methods have advanced so they are now sensitive enough to detect small differences, including those that would be considered clinically meaningful between a biosimilar and a reference product, differences that previously might have created sufficient residual uncertainty for FDA to require comparative clinical studies."

Meanwhile, "clinical efficacy studies using conventional clinical endpoints or PD endpoints generally are not sensitive enough to detect differences between a biosimilar and the reference product that were not observed in early analytical testing or PK studies." Therefore, "in most cases, additional comparative clinical efficacy studies offer no meaningful, new, or actionable information for the regulatory decision-making process and should not be required."

The FDA should retain the ability and flexibility to request additional evidence – such as a comparative clinical efficacy study – before approval, "but it should only do so when scientifically justified and unique risk-based considerations are identified considering," the paper suggests. "For example, the mechanism of action, the complexity of the product, or the delivery mechanism."

These requests "should be the exception rather than a generally applied rule, and FDA should discourage the conduct of comparative efficacy studies when analytical, functional, and PK

methodologies are sufficient to detect clinically meaningful differences."

Global Comparator Would Eliminate 'Duplicative Testing'

Meanwhile, the paper's second request – to "establish global regulatory comparators to support demonstration of biosimilarity" – should see FDA "work with other regulatory authorities to establish global comparators that would eliminate the need for duplicative PK testing of reference products from different regions of the world to support the requirements of various health regulatory authorities when sponsors seek to use data comparing a proposed product with a non-US-approved comparator product to support a demonstration of biosimilarity."

Currently, if a biosimilar sponsor seeks to use data comparing its candidate with a non-US comparator product to support a demonstration of biosimilarity, the FDA "expects the sponsor to provide adequate data or information to establish an acceptable bridge to the US-licensed reference product," the position paper notes. "For example, typically, FDA requires PK studies that include the biosimilar and both the FDA-licensed and EU-approved reference biologics."

But including "both the FDA-licensed and EU-approved reference products in PK studies is usually unnecessary if the versions of biologics licensed in different jurisdictions with similar scientific and regulatory standards share the same development data." In these cases, "a global comparator can be established eliminating the need for duplicative testing of multiple reference products to support the requirements of various health regulatory authorities."

"Establishment of a global comparator in the US and other jurisdictions is well-supported scientifically," the paper underlines, "and in practice and would help to make high quality biosimilars available for patients more quickly and at lower cost without any compromise of safety or effectiveness."

Ultimately, the AAM concluded, the position paper's recommendations "will not lower safety, efficacy, or quality standards," and "nor will they involve an extensive revision of the existing regulatory framework related to biosimilars."

Global Regulators Move Towards Streamlined Pathways

The Biosimilars Council's suggestions reflect wider global moves towards more streamlined pathways for biosimilar registration that would not necessarily require comparative clinical efficacy studies.

Most prominently, the European Medicines Agency recently concluded a consultation on the subject, with the agency conceding that there was a need to re-evaluate the need for comparative efficacy studies, which the EMA said was "increasingly questioned in general" (*see sidebar*).

The agency's Biosimilar Medicinal Products Working Party has pledged to "take account of all

comments received during the public consultation on the concept paper" to prepare a subsequent draft reflection paper. This will then be published for a further six-month public consultation period, after which "BMWP will take account of all comments received during the public consultation on the draft reflection paper when preparing the final text."

The EMA expects the final reflection paper to come into operation three months after publication following adoption by the agency's Committee for Medicinal Products for Human Use.

EMA Mulls Dropping Comparative Efficacy Trials For Biosimilars

By David Wallace

06 Feb 2024

In a move that could hold major promise for the biosimilars industry, the European Medicines Agency has opened up a consultation on re-evaluating the need for comparative efficacy studies to support biosimilar applications.

Read the full article here

Meanwhile, US regulators are also considering moves in a similar direction. Last year, Sarah Yim – director of the FDA's Office of Therapeutic Biologics and Biosimilars – asked during a public workshop on reevaluating the need for biosimilar comparative efficacy trials if there was a way for regulators to confidently give advice early in development that clinical studies would not be required.

"Can we do more of a dichotomous kind of assessment where we think 'OK, if you can reach highly similar with your BLA then the clinical study might not be needed?'" she mooted. "Do we even have enough information to make that kind of assessment early in development when folks are asking these clinical questions?" (Also see "*Biosimilar Clinical Trials: How Can Regulators Determine Waiver Early In Development?*" - Generics Bulletin, 19 Sep, 2023.)

The FDA has previously issued guidance lifting the comparative efficacy study requirement for approval of insulin biosimilars, but Yim had historically suggested that a broad ruling extending it to all products was unlikely. (Also see "*US FDA Unlikely To Issue Broad Biosimilar Guidance Saying Comparative Clinical Studies Unnecessary*" - Pink Sheet, 7 Oct, 2021.)

But the biosimilars industry has repeatedly argued that the FDA needs to move with the times and embrace a more streamlined approach to product development, rather than remaining rooted in old thinking dating back to an era in which experience with biosimilars was limited and analytical methods were less sophisticated. (Also see "*That's So 15 Years Ago: Biosimilar Advocates Press US FDA, Sponsors To Evolve Thinking, Streamline Development*" - Pink Sheet, 22 Aug, 2023.)

The UK has previously been something of a trailblazer in this area, several years ago laying out a new approach to its biosimilar licensing pathway that included typically not requiring comparative efficacy data, as well as considering approved biosimilars interchangeable with their reference products for all indications. (Also see "*UK Lays Out Reduced-Data Pathway For Biosimilars*" - Generics Bulletin, 9 Oct, 2020.)

Biosimilars Forum Urges FDA To Change Requirements

The sentiment of the AAM Biosimilars Council's position paper is shared by another US biosimilars industry association, the Biosimilars Forum.

Last year, the group's executive director Julie Reed told *Generics Bulletin* that "the FDA has to step up" and "has got to streamline development. They need to look at the cost and what they're asking for in terms of new biosimilar development" (*see sidebar*).

"The FDA has got to get on the same page as industry," Reed urged. "And I think that's really key because we've got a decade's worth of experience, and we can start to streamline and change the requirements for development."

"And these products will continue to be just as safe and efficacious as they are today, but probably be able to get to the market sooner, which is huge, huge for consumers."

US Biosimilars Need Access In Exchange For Industry Commitment

By David Wallace

18 Jul 2023

As the dust settles after a wave of fresh adalimumab biosimilar launches, the US Biosimilars Forum's executive director Julie Reed talks to *Generics Bulletin* about how other stakeholders need to step up to meet industry's commitment to the sector – as well as how PBMs are distorting the market and streamlined regulation is needed to drive competition.

Read the full article here

"If the FDA doesn't change its requirements, and start to look at streamlining biosimilar development," Reed suggested, "that's a factor into the level of competition and cost savings you're going to see."