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La regulación propuesta por el Ministerio de la Protección Social sería muy similar a la propuesta por la FDA

Biosimilares en dos etapas

Un vocero de FDA comunicó a BioCentury que la FDA adoptará una regulación para el permiso de comercializar biosimilares en los Estados Unidos a través de dos pasos o etapas. La primera revisando la información analítica del biosimilar y el de referencia para establecer si sería necesario extender o no estudios en animales y en humanos laas cuales serían exigidas en una segunda etapa. Esta propuesta establece un paradigma muy diferente al seguido por la Agencia Europea.

La propuesta de la FDA permitiría que los similares tuvieran un importante porción del mercado dado que por sus menores precios y el aval de la FDA sobre su seguridad y eficacia, podrían sustituir los costosos existentes.

Coincidencialmente en Colombia se está discutiendo un reglamentación para biotecnológicos que tiene un enfoque muy cercano al de la agencia norteamericana. También propone dos etapas basadas en los mismos principios (información básica analítica y de caraterización, la cual se evaluaría para determinar si se requerirían estudios pre clinicos y clínicos).

La diferencia consiste en que la comparación con el de referencia sería exigida dependiendo si se trata de un medicamento innovador o un no innovador y otros criterios técnicos y farmacológicos. La evaluación de la información tendría que ser realizada por un comité de expertos de alta calidad técnica y libres de conflictos de interés.

Esta coincidencia pondría a Colombia en la vanguardia de las regulaciones de América Latina, la mayoría de las cuales establecen rutas diferentes para la aprobación de bioterapéuticos innovadores y competidores.

Cabe recordar que la entrada de biosimilares al mercado favorece la competencia y ayuda a disminuir los precios altos característicos de este tipo de productos. Así, se evitan los monopolios y se favorece el acceso a estas medicinas, críticas para el tratamiento de enfermedades como cáncer, artritis reumatoidea, entre otras.

Nota completa e información adicional:

Biosimilars two-step

By Steve Usdin
Washington Editor
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FDA's biosimilars pathway officially has been open since enactment of the Patient Protection and Affordable Care Act in March 2010, but biosimilars companies are just starting to get a good idea of what the agency will require.

Senior FDA officials have told BioCentury the agency will create a two-step process. Companies first will submit analytic data showing how similar their compounds are to an FDA-approved innovator version. The agency then will determine on a case-by-case basis how much animal and clinical data are required for approval.

This is fundamentally different from EMA, which has published or announced it is writing guidelines that chart the requirements for developing six classes of biosimilar products (see "The Other Side of the Pond").
Rather than lay out such specific requirements, FDA is creating a pathway that will allow companies with strong analytical capabilities to get biosimilars to market more rapidly, and less expensively, than companies that lean more heavily on clinical comparisons.

It is also becoming clear that both EMA and FDA could impose substantial costs by requiring a biosimilar be compared to an innovator that is approved in the jurisdiction where the biosimilar would be marketed.
This could slow the introduction of biosimilars in the U.S. by companies that were looking for quick, relatively inexpensive development programs based on European clinical and marketing experience (see "Foreign Labels").

It also could hamper the development of globally branded biosimilars.

Step 1: Similarity
A number of prospective biosimilars manufacturers, including companies that manufacture innovator products as well as companies that market biosimilars in Europe, have had preliminary discussions with FDA, the agency's Rachel Behrman said last week on BioCentury This Week, BioCentury's public affairs television program.

Behrman, who is associate director for medical policy in the Center for Drug Evaluation and Research, said the agency will spell out in a series of guidance documents how it will implement a two-step approach to reviewing biosimilars.

At least one guidance will be released before year end, she said in FDA's first media interview on the biosimilars pathway.

Rather than create a standard set of preclinical and clinical data required to demonstrate biosimilarity to a reference product, Berman said the agency first wants to see how strong a case the applicant has made that its product is analytically similar to the innovator and then decide what other data will be required.

"First we have to understand from the analytics everything we possibly can about the molecule," she said. "Once we review and fully understand that information, then we will be able to provide advice on the extent of animal and human testing."

Behrman cited FDA's approval of an application from Momenta Pharmaceuticals Inc.<http://www.biocentury.com/companies/momenta_pharmaceuticals_inc> for a generic version of enoxaparin<http://www.biocentury.com/products/enoxaparin>, a low molecular weight heparin marketed by Sanofi<http://www.biocentury.com/companies/sanofi> as Lovenox<http://www.biocentury.com/products/lovenox>, as an example of the different perspectives FDA and EMA have on the power of analytical characterization.

Enoxaparin, a complex carbohydrate, is regulated as a drug in the U.S., not a biologic. Nonetheless, Behrman cited it as an example of how "we may be able to take the European experience [with biosimilars] and go one step further."

While an EMA biosimilars guideline mandates clinical trials for low molecular weight heparin products, FDA approved Momenta's M-Enoxaparin<http://www.biocentury.com/products/m-enoxaparin> based solely on analytical data (see BioCentury, Aug. 2, 2010).

Regulatory decisions about bio-similars, Behrman said, are driven by an entirely different paradigm than is used to review the safety and efficacy of innovator products. "We already know that the molecule is safe and effective. We are trying to establish that this biosimilar will have the same effect in a patient, without any clinically meaningful differences," she told BioCentury This Week.

Several companies that plan to market biosimilars in the U.S., including Momenta and Novartis AG<http://www.biocentury.com/companies/novartis_ag>'s Sandoz division, have embraced the idea that the degree of analytical similarity should determine the amount of animal and clinical data required to demonstrate biosimilarity. Innovators, however, have not universally embraced the concept (see "Is Comparable Similar?").

Amgen Inc.<http://www.biocentury.com/companies/amgen_inc>, which has recently announced its own biosimilars strategy, is not convinced that any amount of analytic data is sufficient to justify an abbreviated clinical package (see "If You Can't Beat 'Em . . ." A5).

"We are not comfortable with the idea that if you can get an analytical package to look as close as possible [to the reference product] you have sufficiently addressed all the relevant safety issues and must only do limited studies," Gino Grampp, regulatory affairs director at Amgen, told BioCentury. "We think it is important to evaluate safety and immunogenicity over a longer period of time."

Analytic, and possibly clinical, data also will be key to FDA's decisions about whether it will allow a biosimilar to extrapolate from studies demonstrating safety and efficacy for one indication to all of the indications on the innovator's label.

FDA will make decisions on extrapolation on a case-by-case basis, Behrman told BioCentury This Week. These decisions "will depend on the biologic plausibility; it will depend on the population; it will depend on really how close they are," she said.

Extrapolation is an economic incentive for using the biosimilars pathway, rather than attempting to obtain a standard BLA, according to Mark McCamish, head of global biopharmaceutical development for Sandoz.

The U.S. biosimilars pathway "has huge opportunities because of the possibility to extrapolate to multiple indications, and the unique ability in the U.S. to get interchangeability," he told BioCentury. "On the down side, there are critical limitations, including the IP process one has to go through."

The patent litigation section in the U.S. biosimilars law "erects a significant barrier" to using the pathway because it forces biosimilars companies to disclose details on their proprietary manufacturing processes to the manufacturers of reference innovator products, John Engel, a partner at the law firm Engel & Novitt LLP, said on BioCentury This Week.

According to Engel, biosimilars companies will have to decide - "do you want to put yourself in the position where you are turning over your trade secrets to your fiercest competitors? That has been the biggest disincentive as we've been evaluating how companies should proceed with their applications."

Sandoz hasn't disclosed which approach it is taking for specific products. But according to McCamish, the factors will include whether a product "has so many indications that it makes no sense to file a BLA for each. Or does it have a predominant indication," so extrapolation isn't as important.

Step 2: Interchangeability

Even more than extrapolation of indications, the potential to have a product classified as interchangeable with the innovator - and hence potentially automatically substitutable - is the biggest potential upside to using the FDA pathway, according to McCamish.

If biosimilar interchangeability works like generic drug interchangeability, it would allow biosimilars to rapidly capture most of the innovator's market share with minimal marketing.

According to Behrman, FDA views approval of a biosimilar and classifying it as interchangeable as sequential steps. To accomplish the second step, she said, sponsors will have to surmount high hurdles, including demonstrating the safety of switching back and forth between a biosimilar and an innovator.

"I would have to be comfortable as a physician, we would have to be comfortable as regulators, that a person could go back and forth and back and forth without any compromise in the safety or efficacy of the product to declare it interchangeable," Behrman said. "That is doable, but that is sequentially a step after biosimilarity has been established."

Whether it is part of initial approvals or requires a separate submission after a product has been on the market, several companies that hope to get into the U.S. biosimilars marketplace say they expect to obtain interchangeability.

For example, Momenta's corporate strategy is based on the belief that "we can go after substitutable biologics and that analytics are really going to be the core towards what's going to drive to that strategy," Craig Wheeler, Momenta's president and CEO, said at the Deutsche Bank healthcare conference last week.
In contrast, James Daly, SVP of North American commercial operations at Amgen, told the conference that he "wouldn't anticipate interchangeability with biosimilars."

Referring to Behrman's comments on BioCentury This Week, Daly added: "There was some concern in the last few days on the Lovenox implications as an analog. There's a world of difference between Lovenox and large complex proteins. There really is - in terms of analytics, in terms of the ability to show comparability."
Daly concluded that the generic enoxaparin approval was based on a "sameness criteria that is literally impossible for biologics, for large molecules."

Speaking on BioCentury This Week, Behrman noted there has been some "inadvertent switching" among biosimilar and innovator biologics in Europe.
Amgen's Grampp said it is important to "differentiate between switchability and interchangeability" of biosimilars.

"There are five or six or seven ESAs in Europe. Many have shown you can switch from one product to another under the supervision of a physician," he said. "Our concern with interchangeability is that it could be occurring multiple times and essentially blinded to the physician or patient."

SCOTUS wildcard
While the scientific standards FDA will use to review biosimilars applications are slowly coming into focus, companies investing in biosimilars for the U.S. market have to factor in a possible wildcard: several lawsuits pending in federal courts that challenge the constitutionality of the Patient Protection and Affordable Care Act.
If the U.S. Supreme Court ultimately rules that provisions of the act are unconstitutional, it would also have to determine if those portions can be separated from the overall law, Daniel Kracov, a partner at the law firm Arnold & Porter LLP, said on BioCentury This Week. If not, the entire law, including its biosimilars provisions, could be scrapped.

Momenta noted this possibility in a March 10 SEC filing, reporting that if the "legislation is declared unconstitutional, is significantly amended or is repealed, our opportunity to develop biosimilar (including interchangeable) biologics could be lost and our business could be materially and adversely affected."

COMPANIES AND INSTITUTIONS MENTIONED

Propuesta Colombiana: www.minsalud.gov.co

Amgen Inc.<http://www.biocentury.com/companies/amgen_inc> (NASDAQ:AMGN), Thousand Oaks, Calif.
Biogen Idec Inc.<http://www.biocentury.com/companies/biogen_idec_inc> (NASDAQ:BIIB), Weston, Mass.
Bioton S.A.<http://www.biocentury.com/companies/bioton_sa>, Warsaw, Poland
Eli Lilly and Co.<http://www.biocentury.com/companies/eli_lilly_and_co> (NYSE:LLY), Indianapolis, Ind.

European Medicines Agency<http://www.biocentury.com/companies/european_medicines_agency> (EMA), London, U.K.
Genentech Inc.<http://www.biocentury.com/companies/genentech_inc>, South San Francisco, Calif.
Health Canada<http://www.biocentury.com/companies/health_canada>, Ottawa, Canada
Johnson & Johnson<http://www.biocentury.com/companies/johnson_and_johnson> (NYSE:JNJ), New Brunswick, N.J.
Momenta Pharmaceuticals Inc.<http://www.biocentury.com/companies/momenta_pharmaceuticals_inc> (NASDAQ:

MNTA), Cambridge, Mass.

Novartis AG<http://www.biocentury.com/companies/novartis_ag> (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc.<http://www.biocentury.com/companies/pfizer_inc> (NYSE:PFE), New York, N.Y.
Roche<http://www.biocentury.com/companies/roche> (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi<http://www.biocentury.com/companies/sanofi> (Euronext:SAN; NYSE:SNY), Paris, France
Teva Pharmaceutical Industries Ltd.<http://www.biocentury.com/companies/teva_pharmaceutical_industries_ltd>, (NASDAQ:TEVA), Petah Tikva, Israel
U.S. Food and Drug Administration<http://www.biocentury.com/companies/us_food_and_drug_administration> (FDA), Silver Spring, Md.