The Food and Drug Administration recently held a public hearing to obtain input on issues and challenges associated with the implementation of the Biologics Price Competition and Innovation Act of 2009. Among those providing testimony at the two-day hearing were pioneer drug companies, potential biosimilar manufacturers, trade groups, patient advocacy organizations, and physicians who treat patients with biologics. The FDA sought and received comments on:

- scientific and technical factors related to a determination of biosimilarity or interchangeability;
- the type of information that may be used to support a determination of biosimilarity or interchangeability;
- development of a framework for optimal pharmacovigilance for biosimilar and interchangeable biological products;
- scope of the revised definition of a “biological product;”
- priorities for guidance development by the FDA;
- scientific and technical factors related to reference product exclusivity;
- scientific and technical factors that may inform the agency’s interpretation of “product class” as it relates to available regulatory pathways for certain protein products during the 10-year transition period following enactment of the BPCIA; and
- the establishment of a user fee program for biosimilar and interchangeable biological products.

The discussions at the hearing highlight the amount of work that still needs to be done to implement a biosimilars review pathway in the United States. A live webcast and recording of the hearing is viewable at https://collaboration.fda.gov/p48258466/ and https://collaboration.fda.gov/p68871994/. The FDA will also accept electronic and written comments until December 31, 2010.

Medicare Reimbursement for Biosimilars

The health care reform legislation enacted in March 2010 included within it the “Biologics Price Competition and Innovation Act of 2009,” (BPCIA) adding Sections 351(k)-(m) to the Public Health Service Act. The BPCIA authorizes the FDA to issue licenses for “biosimilar” products under an abbreviated application that relies in part on data or information in an application for a different biological product (the reference product) already licensed under Section 351 of the PHSA.

The BPCIA instructs the Centers for Medicare & Medicaid Services (CMS) to reimburse payment for a biosimilar at the sum of (1) the average sales price of all National Drug Codes assigned by the FDA for such product, plus (2) 6 percent of the “amount determined” for the reference product (i.e., the lesser of the average sales price or the wholesale acquisition cost). Because of this reimbursement formula, (continued on page IV)
The biotech industry has recently become the latest battleground for the patentable subject matter debate. At issue is the patentability of claims directed to “isolated” DNA molecules. In the past, the patentability of isolated DNA sequences primarily turned on the written description requirement set forth in 35 U.S.C. § 112. For example, in Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559 (Fed. Cir. 1997), the court held that “[a]n adequate written description of a DNA…'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention.” Four years later, the United States Patent and Trademark Office addressed the utility requirement set forth in 35 U.S.C. §§ 101 and 112, by releasing its Final Guidelines For Determining Utility Of Gene-Related Inventions.

Until recently, however, the issue of the patentable subject matter requirement set forth in U.S.C. § 101 went largely unnoticed. That changed on March 29, 2010, when Judge Sweet of the Southern District of New York issued his opinion in Assoc. For Molecular Pathology v. U.S.P.T.O., 702 F. Supp. 2d 181 (S.D. N.Y. 2010) (commonly referred to as the ACLU v. Myriad case), which in no uncertain terms held that isolated DNA was not patentable subject matter and was instead merely a “product of nature.”

According to the court in ACLU v. Myriad, the PTO grants patents on “isolated DNA” under the standard patentable subject matter jurisprudence related to isolated chemical compounds. Noting that “scientists in the fields of molecular biology and genomics have considered this practice a ‘lawyer’s trick,’” the court explains that it is premised on the PTO’s view that DNA should be treated no differently from other chemical compounds and that purification from its natural state in the body is the “transformation” giving rise to patentability. Id. at 185.

Expressly rejecting the PTO’s view, and noting that it owes no deference to the PTO, the court stated that “patentable subject matter must be ‘markedly different[1]’ from a product of nature” and held that the “claimed isolated DNA is not ‘markedly different’ from native DNA.” Id. at 221-229. Undaunted by the impact that such an opinion may have on the thousands of issued DNA-related patents, the court notes that the Federal Circuit had issued its opinion in In re Bilski, which “set out a test for the patentability of method claims that potentially will invalidate thousands of patents on business method[s].” Id. at 221.

At the end of the day, ACLU v. Myriad was a district court opinion and therefore did not instantly invalidate thousands of issued patents. The Federal Circuit, however, is beginning to make its opinion known on the issue, and it appears there may be a split of opinion on the court related to the patentability of isolated DNA.

On August 4, 2010, a three-judge panel consisting of Circuit Judges Bryson, Dyk, and Prost issued its opinion in Intervet Inc. v. Merial Ltd., No. 2009-1568 (Fed. Cir. Aug. 4, 2010), which related to patent claims directed to “an isolated DNA molecule.” While the majority opinion vacated the district court’s entry of summary judgment of noninfringement without considering the question of patentable subject matter, Circuit Judge Dyk picked up the issue in a separate opinion. In particular, Dyk explained that the claim directed to isolated DNA “raises substantial issues of patentable subject matter” because “allowing the patenting of naturally occurring substances preempts the use by others of substances that should be freely available to the public.” Judge Dyk continued, “[I]t appears that in order for a product of nature to satisfy section 101, it must be qualitatively different from the product occurring in nature, with ‘markedly different characteristics from any found in nature’” and “it is far from clear that an ‘isolated’ DNA sequence is qualitatively different from the product occurring in nature.”

This question is sure to wind its way up through the courts and may be the next hot Federal Circuit issue. To be sure, it will be interesting to see how the Federal Circuit confronts the issue when it is squarely before it and whether the Supreme Court and even Congress will decide to make their opinions on the matter known.
# Pending Biologic Cases as of October 2010

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Impact of the New Biosimilars Legislation on Biologic Filings

With the ink now dry on the Biologics Price Competition and Innovation Act of 2009, the reaction by likely applicants has, not surprisingly, been mixed, with some companies eschewing it, some embracing it and others adopting a wait-and-see approach.

Sandoz, for example, has opted to pursue approval of biosimilars through traditional channels, such as BLAs and paper NDAs, instead of facing two perceived risks of filing for approval under the Act. The primary risk Sandoz cites is that the Act requires very early disclosure to relevant pioneer companies of biosimilar applications and “other information” relating to the imitator’s manufacturing processes, which, according to Sandoz, affords pioneers the opportunity to “pick apart [imitator] arguments scientifically and on the patent front to leverage in their own litigation against [imitator firms]” years before the imitator product comes to market. See “The Pink Sheet,” May 3, 2010, at p. 7. Additionally, Sandoz notes that the Act does not require patent litigation resolution prior to approval of a biosimilar, which could result in prolonged patent litigation and substantial additional costs to the imitator. See id.

By contrast, it has been reported that Merck has filed or is planning to file an application with the FDA via the new biosimilar approval pathway. According to Merck BioVentures President Michael Kamarck, “[w]hen regulators create a pathway like this one they are actually asking you to help them, to really carve what the space looks like. We see that only as opportunity.” See “The Pink Sheet,” July 5, 2010, at p. 3.

Teva, Pfizer, Genzyme and most other companies have adopted a wait-and-see strategy for filing biosimilar applications under the Act. Teva, for instance, is currently utilizing the BLA process for its biosimilar products, but the president and CEO of Teva North America, Bill Marth, said “[a]s the FDA determines the process for filing an abbreviated BLA, we will continue to evaluate what pathway we take on a protein-by-protein basis.” See “The Pink Sheet,” May 3, 2010, at p. 7.

Many thought that an abbreviated biosimilar approval pathway would significantly alter the biopharmaceutical industry, but the Act has had minimal impact to date, likely because of stakeholders’ mixed reactions and because the FDA has yet to issue guidance on how it will implement the Act. Regarding the latter, and as noted in this newsletter, the FDA held a public hearing on November 2-3, 2010, to solicit comments on how approval of biosimilars should be effected. Electronic and written comments are also being accepted by the FDA until December 31, 2010. Until the FDA can digest this commentary and issue its guidance, it is unlikely that a majority of biopharmaceutical companies will participate in the new approval process.

Medicare Reimbursement for Biosimilars

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manufacturers that have a choice should choose the reference product with the greatest Medicare reimbursement. And while perhaps the reimbursement formula is seemingly straightforward enough, as is often the case, the definitions of some of these terms can be quite complicated, as discussed below.

“Average Sales Price” Calculation for Biosimilars

In general, the ASP is the volume-weighted average of the average sales prices for all products included within the same “multiple source drug” billing and payment code, determined by:

(1) computing the sum, for each National Drug Code assigned to such products, of (a) the manufacturer’s average sales price determined by the Secretary of Health and Human Services (without dividing such price by the total number of billing units for the National Drug Code for the billing and payment code) multiplied by (b) the total number of units (such as capsules, tablets, milligrams, or molecules) specified by the manufacturer sold; and

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(2) dividing the amount under (1) above by the sum, for each National Drug Code assigned to such products, of (a) the total number of units specified by the manufacturer sold multiplied by (b) the total number of billing units (the identifiable quantity associated with a billing and payment code as established by the Secretary of HHS) for the National Drug Code for the billing and payment code.

The payment amounts shall be updated on a quarterly basis and shall be applied based upon the manufacturer’s average sales price calculated for the most recent calendar quarter for which data is available.

The “manufacturer’s average sales price” is defined as (a) total sales to all purchasers in a calendar quarter in the United States for the product divided by (b) the total number of units of the product sold by the manufacturer in the quarter. The total sales include volume discounts, prompt pay discounts, cash discounts, free goods that are contingent on any purchase requirement, chargebacks, and most rebates. The Secretary of HHS may include in the average sales price other price concessions, which may be based on recommendations of the Inspector General, and that would result in a reduction of the cost to the purchaser.

Special provisions apply during the first quarter of sales where data on sales prices may not be sufficiently available. Quarterly calculations may also be adjusted based on lag in the reporting of information. Excluded from the calculation are sales exempt from “best price” and sales at “nominal charge,” as defined in the Public Health Service Act.

“Amount Determined” Calculation for Reference Product

The “amount determined” for the reference product (upon which the 6 percent addition to the ASP is based for reimbursement) is the lesser of (a) the average sales price for all National Drug Codes assigned to the reference product using the formula described above and (b) the “wholesale acquisition cost” for all National Drug Codes assigned to such product.

The “wholesale acquisition cost” is defined as the manufacturer’s list price for the drug or biological to wholesalers or direct purchasers in the United States, not including prompt pay or other discounts, rebates, or reductions in price, for the most recent month for which the information is available, as reported in wholesale price guides or other publications of drug or biological pricing data. The same volume-weighted methodology for calculating the average sales prices is used to calculate the wholesale acquisition cost.

Clearly, the process for calculating the reimbursement for biosimilars is not a simple exercise. There are many complexities, and manufacturers should take care when determining the likely reimbursement rates for any particular product.

Medicare Coverage Determinations

Of course, to be eligible for Medicare reimbursement in the first place, there must be a “coverage determination” finding that use of an item or service is “reasonable and necessary.” Most decisions as to whether to provide coverage are made at the local level by clinicians at the contractors that pay Medicare claims, such as BlueCross BlueShield. A list of existing contractors and local coverage determinations is available on the CMS website.

In most cases the reference product will likely have already been through the coverage determination process, paving the way for reimbursement for the biosimilar product. However, for those rare occasions when the biosimilar product leads the way at CMS, manufacturers seeking a local coverage determination should contact a local contractor to determine the relevant information.

In certain cases, CMS may deem it appropriate to develop a national coverage determination (NCD) for an item or service to be applied on a national basis for all Medicare beneficiaries meeting the criteria for coverage. CMS initiates the NCD process by “opening” the NCD via a posting on the CMS coverage website. Development of a complete, formal request for an NCD can be initiated either by an outside party or internally by CMS staff. Outside parties are encouraged by CMS to engage in preliminary discussions with the agency regarding issues that may affect review of their requests. A requestor may be a Medicare beneficiary, manufacturer, provider, supplier, medical professional association, health plan, or any other party.

CMS itself may initiate an NCD in certain circumstances, including but not limited to:

- The health technology represents a substantial clinical advance and is likely to result in a significant health benefit or a significant impact on the Medicare program.

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• Providers, patients or other members of the public have raised significant questions, supported by CMS’s initial review of available data, about the health benefits of currently covered items or services, specifically regarding the Medicare population.

• Local coverage policies are inconsistent to the detriment of Medicare beneficiaries, such as when the variation is not related to local differences in the capabilities of health care providers to use the technology effectively which can be resolved over time through provider training and education or through the local coverage process.

CMS may request an external “technology assessment,” the primary purpose of which is to evaluate the clinical and scientific evidence pertaining to the clinical benefits and risks of the technology. Certain issues may also be referred to the Medicare Evidence Development and Coverage Advisory Commission (MEDCAC).

If neither a technology assessment nor referral to the MEDCAC is necessary, CMS has six months to render a proposed decision on a request for coverage. If a technology assessment or referral to the MEDCAC is made (and no clinical trial is requested), CMS has nine months to issue a proposed decision. The proposed decision is posted on the CMS website (or other appropriate means) for a 30-day public comment period. A final decision will be issued not later than 60 days after the conclusion of the comment period.

While the necessity for an initial Medicare coverage determination for a biosimilar should be rare, familiarity with the process will help manufacturers understand the broader market in which they operate and may even become part of a regulatory strategy seeking to maximize reimbursement.