# Reports

This part of the EJRR hosts reports in which our correspondents keep readers up to date on the most recent developments in different areas of risk regulation. Our aim is to fuel the debate and trigger future research on cutting-edge risk subjects. The Reports are organised under different policy sections. Further sections will be added at regular intervals. If you are interested in contributing to any of the existing sections, please contact the Reports Editor at enrico.bonadio.1@city.ac.uk

## Biotechnology

*This section aims to update readers on decisions related to marketing products of modern biotechnology (e.g., GMOs, animal clones) at EU level and on national measures concerning their production. Special attention is devoted to problems of competence between Member States and the EU in regulating biotechnology issues; the institutional dynamics of decision making regarding products derived from modern biotechnology; the relationship between the EFSA and the EU institutions on green biotech-related issues; the evolution of EU regulatory framework and of national attitudes towards the risks and benefits of biotechnology derived products and their production. This section will also delve into the interaction between the EU legislation and WTO law regarding advances in the application of biotechnology within the agri-food value chain.*

### Biosimilars: Current situation and future expectations

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#### I. Biosimilars definition. Global need for biotherapeutics

Biotherapeutics, also known as biomedicines, biopharmaceuticals or biotechnology products, can be used for the augmentation or replacement of naturally occurring proteins in numerous pathological conditions, including common diseases and rare genetic conditions. Currently, the two mature biotherapeutic sectors are recombinant protein therapeutics (rDNA proteins) and monoclonal antibodies (mAbs), which are set to generate more than 90% of total sales from 2010–2015. Examples of biotherapeutics include human erythropoietin (Erypo®) human insulin (Humulin®), rituximab (Rituxan®); human growth hormone (Genotropin®) and tumor necrosis factor-alpha blockers such as adalimumab (Humira®), etanercept (Enbrel®) and infliximab (Remicade®)[1]. Despite the fact that they represent one of the most dynamic and promising segments of the pharmaceutical industry[2] and an impressive contribution in health care, patient access to these products is often limited by their high costs, particularly in developing countries. It has been reported that the cost of these products, which can range from $15,000 to $100,000 per year of treatment, is much higher than the cost of traditional small-molecule products, which implies important economic challenges to guarantee their affordability[3].

The increasing focus on cost containment and the expiration of patents for the first major group of originator´s biotherapeutics have preceded the emergence of products that are designed to be "similar" to a licensed originator or innovator product. Several terms, such as "biosimilar products", "follow-on protein products", "similar biological medicinal products" and "subsequent-entry biologics" have been employed by different jurisdictions to describe them. Biosimilars have been defined as products that are

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1 Bao-Lu Chen, "CMC Issues and Regulatory Requirements for Biosimilars", 5 *Trends in Bio/Pharmaceutical Industry* (2009), pp. 19 *et sqq.*, at p. 19.

2 Steven Simoens, "Biosimilar medzicines and cost-effectiveness", 3 *ClinicoEconomics and Outcomes Research* (2011), pp. 29 *et sqq.*, at p. 30.

3 Brent R. Williams and David Wenyan Shen, "Current Considerations for Biosimilar Therapeutics ", 5 *Trends in Bio/Pharmaceutical Industry* (2009), pp. 8 *et sqq.*, at p. 9.

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similar but not identical, in terms of quality, safety and efficacy to an approved biological product. That allows the applicant to rely on certain existing scientific knowledge about the biological medicine that has already been authorized[4].

## II. EU Biosimilar Guidelines

The concept of "Similar Biological Medicinal Products" was introduced in Europe in 2003 by the amendment to Annex I of Directive 2001/83/EC, setting the legal basis for its marketing authorization[5]. Since then, the EMA (European Medicines Agency) has published specific guidelines on similar biological medicinal products containing recombinant somatropin[6], granulocyte-colony stimulating factor[7], insulin[8], erythropoietin[9], interferon alpha[10] and low-molecular-weight-heparins[11] while concept papers for similar biological medicinal products containing recombinant interferon beta[12], follicle stimulating hormone[13] and monoclonal antibodies are already available[14].

According to the regulatory guidelines developed for the European Union one of the key paradigms for biosimilars is that the clinical data required at approval are limited. This is an important issue since it represents a significant reduction in development costs, making biosimilars production a viable business. Nonetheless, and because of the potential risks associated with biotherapeutic products, there is a need for a rigorous risk management plan and pharmacovigilance program with respect to efficacy and safety during the post-approval period.

Another important aspect in biosimilars approval process relies on therapeutic indications, which may be extended if justified. EMA accepts that if the biosimilar shows adequate comparability to the innovator or original product for one indication, it is reasonable to extend the approval of the biosimilar to other indications of the innovator product. That is important in order to select the most sensitive conditions for the design of a comparative trial. Omnitrope (marketed by Sandoz) is a biosimilar version of the reference product Genotropin (manufactured by Pfizer). Like Genotropin, Omintrope is a recombinant human somatropin produced from *E. coli*. The EMA approval of this biosimilar included indications for which it has not been evaluated in clinical trials, based on extrapolation of data from the reference product. Thus, the comparability of Omnitrope to Genotropin was demonstrated in a randomized controlled trial in children with lack of growth hormone with an additional safety study performed also in children, while the approval of Omnitrope included extrapolation of these clinical data to adults with pronounced growth hormone deficiency[15].

Nowadays, there are more than ten biosimilar products in the European market without reports of adverse incidents and it has been estimated by the European Generic Medicines Agency that biosimilars savings in the European Union were around €1.4 billion in 2009[16]. Nevertheless, demonstrating bio-

4 Georg-Burkhard Kresse, "Biosimilars – Science, status, and strategic perspective", 72 *European Journal of Pharmaceutics and Biopharmaceutics* (2009), pp. 479 *et sqq.*, at p. 479.

5 Directives 2003/63/EC of the European Parliament and of the Council of 25 June 2003 and 2004/27/EC of the European Parliament and of the Council of 31 March 2004, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

6 EMEA, Annex to guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: non-clinical and clinical issues . Guidance on similar medicinal products containing somatropin. EMEA/CHMP/BMWP/94528/2005, 2006.

7 EMEA, Annex to guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte colony stimulating factor. EMEA/CHMP/BMWP/31329/2005, 2006.

8 EMEA, Annex to guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin. EMEA/CHMP/BMWP/32775/2005, 2006.

9 EMEA, Annex to guideline on similar biological medicinal products containing biotechnology –derived proteins as active substance: non-clinical and clinical issues . Guidance on similar medicinal products containing recombinant erythropoietins. EMEA/CHMP/BMWP/301636/2008, 2010.

10 EMEA, Reflect ion paper: non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha. EMEA/CHMP/BMWP/102046/2006, 2009.

11 EMEA, Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins. EMEA/CHMP/BMWP/118264/2007, 2009.

12 Concept paper on similar biological product containing recombinant interferon beta. EMA/CHMP/BMWP/86572/2010. Deadline for comments: 11 June 2010.

13 Concept paper on similar biological product containing recombinant follicle stimulating hormone. EMA/CHMP/BMWP/94899/2010. Deadline for comments: 1 June 2010.

14 Guideline on similar biological medicinal products containing monoclonal antibodies (Draft). EMA/CHMP/BMWP/403543/2010. End of consultation: 31 May 2011.

15 EMA, "Scientific Discussion: marketing authorisation for Omnitrope (Sandoz GmbH)", 2006, available on the Internet at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_- _Scientific_Discussion/human/000607/WC500043692.pdf> (last accessed on 16 April 2012).

16 European Generic Medicines Association, "Vision 2015: the EGA 's thoughts on how to improve the legal and regulatory framework for generic and biosimilar medicines ", 2010, available on the Internet at: <http://www.egagenerics.com/doc/EGA_Vision_2015.pdf> (last accessed on 16 April 2012).

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similarity is not simple and it has been reported that the average cost of bringing a biosimilar to a highly-regulated market is around $75–$250 million[17]. Head-to-head studies must be run, that is comparison to the reference product including both physicochemical and functional characterization data in addition to non-clinical and clinical data. A comparability exercise needs to demonstrate that the biosimilar and the reference product have similar profiles with respect to product quality, safety and efficacy. That is accomplished through analytical studies, examining physical properties, aminoacid sequence, high order structures and post-translational modifications.

*In vitro* or *in vivo* potency assays must demonstrate comparable activity and additionally levels of product related and process related impurities need to be assessed and quantified.

If differences are present between the biosimilar and the reference biologic product on product impurity and stability profile, these differences have to be justified using scientific knowledge or preclinical or clinical studies. Also, clinical studies should be designed to demonstrate equivalence rather than non-inferiority, i.e., a "better" outcome is not an option because it indicates lack of similarity.

Moreover, in some cases the Committee for Medicinal Products for Human Use of EMA had adopted a negative opinion on the Marketing Authorization Application presented by a biosimilar sponsor on the grounds of major concerns on quality issues or non-clinical issues. In such circumstances, this organism recommended the refusal of the marketing authorization since there were differences identified in the impurity profile between the two products, insufficient stability data, and inadequate validation of manufacturing process for the drug product or different response in clinical trials[18]. In other cases the application was withdrawn by the sponsor after day 120 of the Centralized Procedure. At this point the company is expected to respond to the list of questions and objections drafted during the assessment process by the Committee for Medicinal Products for Human Use[19].

## III. Worldwide situation

Biosimilars have been in the market of several countries like Argentina, India, Brazil, Mexico among many others for a long time. This has been extraordinary useful for facilitating patient access to numerous disease treatments with biotherapeutics. It has occurred thanks to an adequate legal framework on intellectual property, specific of each country, and in certain cases by virtue of an important local scientific development and recombinant protein manufacturing skills. It is clear that the decision on biosimilar use and regulation can only be taken at a national or possibly regional level. In 2009, a WHO Expert Committee on biological Standardization issued guidelines, largely based on EMA´s guidelines, to promote global consensus on the regulation of biosimilars, assist in their registration based on an abbreviated regulatory process taking into account the claim of similarity to a reference product and in this manner improve the availability of safe and effective biosimilar products worldwide[20]. There is no doubt about EMA´s pioneering work to introduce a regulatory framework for biosimilars and to facilitate market entry and competition for off patent medicines. This has provided also a scientific approach to avoid unnecessary risks for patient safety and unnecessary or even unethical animal or humans trials. On this basis other country regulatory authorities have developed their own guidelines for biosimilars approval. That is the case of Japan, Canada, Switzerland, Turkey and Brazil. In Australia, for example, the EMA guidelines were adopted without changes.

The United States is still in the process of implementing a regulatory pathway for biosimilars, or follow-on biologics as they have been specifically named in that country. The Food and Drug Administration (FDA) is the authority that accepts, reviews and approves license applications for biosimilar products, and is working to establish procedures and create a mechanism to review applications. Recently, three draft guidance documents have been published in order to carify expectations and provide predictability to sponsors initiating biosimilar

17 Mark McCamish and Gillian Woollett, "Worldwide experience with biosimilar development, 3 *mAbs* (2011) pp. 209 *et sqq.* at p. 211.

18 EMEA, Refusal assessment report for Alpheon. International Non-proprietary Name: recombinant human interferon-alfa-2a. Procedure No. EMEA/H/C/000585, 2006.

19 EMEA, Press release. Marvel LifeSciences Ltd withdraws its marketing authorisation applications for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel. Doc. Ref. EMEA/2435/2008, 2008.

20 WHO, Expert Committee on Biological Standardization. Geneva, 19 to 23 October 2009, "Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)", 2009, available on the Internet at: <http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/Guidelines_Biotherapeutic_pr oducts_FINAL_HK_IK_12_June.pdf> (last accessed on 16 April 2012).

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development programs. These documents, entitled "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*"[21], *"Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product"*[22] *and "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009"*[23] *refer among other topics to the preferred approach that FDA intends to use to determine biosimilarity including analytical factors to consider during the demonstration that a proposed biosimilar is highly similar to an already approved reference product.* These documents were largely expected since the Patient Protection and Affordable Care Act, signed into law in 2010, amended the Public Health Service Act and created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This pathway is provided in the part of the law known as the *Biologics Price Competition and Innovation Act* (BPCI Act).

The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the "Hatch-Waxman Act"). This US regulation sustained the strong growth of the generic pharmaceutical industry to the point that 7 in 10 prescriptions filled in the United States are for generic drugs[24]. The perspective of extrapolation of this successful initiative in the US from small molecules to biological products has not been free of debate and controversy for many stakeholders, including the branded pharmaceutical industry, biosimilar pharmaceutical firms, scientific researchers, government officers, employers facing rising health care costs, pharmacy benefits managers, patient groups, as well as academics. Biosimilars detractors have emphasized that the generic paradigm cannot be applied to biotherapeutics in an analogous manner because of their complexity. It is accepted that proteins are complex, heterogeneous and unstable in nature, they come from complex manufacturing process and degradation pathways sometimes are not clearly understood[25]. In addition, there are many processes and product related impurities, some of which can be immunogenic[26]. Yet, it is important to note that nowadays a tremendous set of tools is available to perform comparability, since both analytical testing and biological assays are able to detect small differences in molecular conformation[27], degradation products and product heterogeneity[28].

## IV. Comparability concept

Biotherapeutic product manufacturers sometimes may need to introduce changes in the manufacturing process that is used to make a particular product. These changes can be driven for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. Typical examples are increasing manufacturing scale due to increased demand, improving product stability through changes in formulation, replacement of master cell bank, replacement of raw materials which are no longer available, changes in the purification process and removal of animal derived components from the process[29]. All this can result in alterations in product quality that can be minor or major depending on the extent of the manufacturing change[30].

21 *FDA, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", 2012, available on the Internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf >* (last accessed on 12 April 2012).

22 FDA*, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product", 2012, available on the Internet at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf> (last accessed on 12 April 2012).

23 FDA, "Biosimilars: Questions and Answers Regarding Implementation of the Biologic Price Competition and Innovation Act of 2009", 2012, available on the Internet at: < http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf> (last accessed on 12 April 2012).

24 Steven Kozlowski, Janet Woodcock, Karen Midthurn and Rachel Behrman Sherman, "Developing the Nation's Biosimilars Program" 365 *The New England Journal of Medicine* (2011), pp. 385 *et sqq.*, at p. 385.

25 Huub Schellekens and James Bausch, "Biopharmaceutical molecules are not created equally" 268 *The Pharmaceutical Journal* (2002) pp. 300 *et sqq.*, at p. 300.

26 Huub Schellekens, "Biosimilar therapeutics -what do we need to consider?" 2 *Nephrology Dialysis Transplantation* (2009) pp. i27 *et sqq.*, at p. i28.

27 Hongwei Xie, Asish Chakraborty, Joomi Ahn *et al.*, "Rapid comparison of a candidate biosimilar to an innovator monoclonal antibody with advanced liquid chromatography and mass spectrometry technologies" 2 *mAbs* (2011) pp. 379 *et sqq.*, at p. 379.

28 Josephine Grass, Martin Pabst, Martina Chang *et al.*, "Analysis of recombinant human follicle –stimulating hormone (FSH) by mass spectrometric approaches" 400 *Analytical Bioanalytical Chemistry* (2011), pp. 2427 *et sqq.*, at p. 2427.

29 Martin Schiestl, Thomas Stangler, Claudia Torella *et al.*, "Acceptable changes in quality attributes of glycosylated biopharmaceuticas" 29 *Nature Biotechnology* (2011), pp. 310 *et sqq.* at p. 310.

30 EMEA, ICH Topic Q5E Comparability of Biotechnological/Biological Products, CPMP/ICH/5721/03, June 2005, avalaible on the Internet at: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002805.pd> (last accessed on 16 April 2012).

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In 1996 the FDA was the first regulatory authority to provide a mechanism to evaluate the impact of these changes without performing additional trials. It published the Guidance "Demonstration of Comparability of Human Biological Products, including Therapeutic Biotechnology-derived Products"[31] which stipulates that comparability assessment is required to support manufacturing process changes without performing additional clinical studies to demonstrate safety and efficacy. A hierarchical risk-based approach is recommended, starting with an extensive "comparability exercise". That includes analytical comparison of post-change product and pre-change product, followed by biological characterization and, if needed, in vivo pharmacokinetic (PK), pharmacodynamics (PD), safety and/or efficacy studies. The need for an *in vivo* study and the type of study required will depend on the magnitude and the potential impact of the changes. In other words, regulatory pathways imply that comparability exercise for postchange products is expected to cover a complete physicochemical and biological analysis followed by preclinical and clinical studies on a case by case basis. If the quality attributes of a product after a manufacturing change deviate from those of pre-change product, this should increase pre-clinical and clinical study requirements. On the contrary, when a product remains within approved specifications after a change, it suggests that the pre- and post-change products are comparable and therefore the changes in the manufacturing process can be made without additional preclinical o clinical studies. Thus, according to FDA the term "comparable" applies to a product after a manufacturing change to an already approved product.

These concepts were extended by EMA with minimal modifications from process changes and product changes made by one company to comparable products produced by a different sponsor. In this case the product is called biosimilar, and it must undergo a comparability exercise with the reference product using a range of biological, physicochemical and immunological procedures.

Some biosimilar proponents also rely on the concept of changes on product quality to argue that the "goalposts" for biosimilarity should be based on the variability of innovator products over time and across batches. They also advocate for a case-by-case approach to approval, rather than product or even biosimilar-wide standards and rules[32]. Even taking into account the recent advances in US regulations on biosimilarity determination some authors have pointed out the difficulties for biosimilars approval in US, mainly due to multiple restrictions for the abbreviated Biologic License Application (aBLA) pathway[33]. The aBLA is an option for approval of biosimilars according to BPCI Act. It requires the disclosure and publication of the full dossier of the biosimilar manufacturer preparing the way for the innovator o even third parties (universities, other companies) to file infringement suits. In contrast, by filing through the full Biologic License Application (BLA) process, the biosimilar manufacturer´s dossier and other data remain proprietary and therefore the biosimilar manufacturer does not need to give the innovator (or anyone else) the full details of its filing nor manufacturing process. Moreover, since litigation from the innovator is not acceptable "without reasonable assertion", without access to the full dossier or details of the biosimilar developer´s manufacturing process it is unlikely that the innovator (or other third party) is acquainted with the "reasonable assertion" requirement[34].

Despite these discussions, many experts predict that biosimilars business will grow significantly, mainly in developed countries. Revenue from the sale of biosimilars is expected to grow from $311 million in 2010 to $2.5 billion in 2015. With this lucrative market, it is no surprise that large pharmaceutical companies are giving signals of interest in these products. Some of these companies reached agreements with other enterprises with a strong knowhow in biosimilars development and production in concordance with well-built manufacturing expertise of required export quality. For example, Pfizer announced in October 2010 a strategic global agreement for worldwide commercialization of biosimilar insulin and analogous products with the

31 FDA, "Demonstration of Comparability of Hu man Biological Products, Including Therapeutic Biotechnology-derived Products", 2006, available on the Internet at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm> (last accessed on 16 April 2012).

32 Sandoz, " Global biosimilar leader Sandoz testifies for Novartis at FDA hearing on US biosimilar pathway", 03 November 2010, available on the Internet at: <http://www.sandoz.com/media_center/news/2010/press_releases/2010_11_03_sandoz_testimony.html> (last accessed on 16 April 2012).

33 Claudia Wiatr, " US Biosimilar Pathway Unlikely to be used. Developers will opt for a traditional BLA Filing", 25 *Biodrugs* (2011) pp. 63 *et sqq.*, at p. 63.

34 Jacqueline Wright Bonilla and Nathan Beaver, "The New US Biosimilar Legislation, One Year Later", 9 *Bioprocess International* (2011), pp. 22 *et sqq.*, at p. 24.

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Indian biotechnology company Biocon. Under this agreement, Pfizer will make upfront payments totalling $200 million to Biocon for exclusive rights to the insulin and insulin analogous products globally, with certain exceptions[35]. Pfizer is not alone in its biosimilar intentions. Merck has also developed a biosimilar division, Merck BioVentures. Merck also plans to have five biosimilar programs in Phase III development by 2012[36].

## V. Concluding remarks

Many countries have already implemented a rigorous program based on scientific principles that evaluates the comparability of biosimilar and innovator products through analysis of molecular structure, biological activity, functional pharmacokinetic parameters, degradation profile and limited clinical trials.

Variations among batches of biopharmaceutical products are attributable to these products complexity and manufacturing processes changes over the product life cycle. The comparability exercise was introduced in the 90´s by the FDA to allow manufacturers of biological products to implement changes in the manufacturing process, in most cases without performing additional clinical trials. The EMA extended the scope of this comparability exercise to biological therapeutics produced by different manufacturers, creating a mechanism for comparability between originator and biosimilar products. If differences are present, regulatory processes intend to quantify and understand the effects, leading to the evaluation of requirements for clinical trials.

EU guidelines have resulted in the approval of more than ten biosimilars with comparable efficacy and safety profiles of their respective reference originator biotherapeutics. Moreover, additional biosimilar approvals are expected in Europe, not only in the classes where biosimilars are already approved, but in in other classes, as monoclonal antibodies.

These precedents have been valuable in the process of approving biosimilars in the rest of the world, including the US. In this country biosimilar products have not been approved yet but new regulation opens the door for different biosimilar sponsors to present their applications. It is expected that the first biosimilars approved in the US will be those that are currently being sold in Europe, for which there is already significant clinical trial information and post marketing surveillance.

It is predictable an increase in the number of collaborations acquisitions and joint ventures between companies that want to access to the huge biosimilar market. These deals will permit companies to leverage pipelines and geographical presence, thereby driving overall commercial success of biosimilars in the future.

Finally, since a significant number of biosimilar products are already approved or are under development these agents will undoubtedly play an increasing role in disease management, providing access to high quality, safe and effective biotherapeutics.

35 Lewis Krauskopf and Bharghavi Nagaraju, "Pfizer to sell biosimilar insulins in Biocon deal", 2010, available on the Internet at: <http://in.reuters.com/art icle/2010/10/18/idINIndia -52267720101018> (last accessed on 16 April 2012).

36 Merck, "Merck and PAREXEL Form Strategic Alliance Focused on Clinical Development of Biosimilar Candidates", available on the Internet at: < http://www.merck.com/newsroom/news-release-archive/ corporate/2011_0112.html> (last accessed on 10 December 2011).

# The Product of Nature Doctrine in the Myriad Saga

*Emanuela Gambini**

## 1. The "Myriad Case" in the U.S.: *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*

On March 26, 2012, the U.S. Supreme Court granted the petition for a writ of certiorari on *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.* (the "Myriad case")[1]. This decision vacated the judgment of appeal and remanded the case to the United States Court of Appeals for the Federal Circuit for further consideration in light

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1 See U.S. Supreme Court Order 11-725, 26 March 2012, available on the Internet at <http://www.supremecourt.gov/orders/courtorders/032612zor.pdf> (last accessed on 30 April 2012).

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