Journal of Intellectual Property Rights
Vol 29, September 2024, pp 407-412
DOI: 10.56042/jipr.v29i5.3838

Legal Pathways for Biosimilar: Comparison of Legal Rules in Different Countries

Sivakumar Priyarega[1†] and Ramanathan Natarajan[2]

[1]Department of Chemistry, Saranathan College of Engineering, Tiruchirappalli — 620 012, Tamil Nadu, India

[2]Research and Development, Saranathan College of Engineering, Tiruchirappalli — 620 012, Tamil Nadu, India

Received: 10th July 2023; revised: 16th February 2024

The generics of biologic drugs play a significant role in pharmaceutics and therapeutics owing to their affordability to a group of patients with fatal diseases. Even though the challenges in manufacturing of these drugs are overcome by biosimilar applicants, the disputes on patents hamper the market entry of biosimilar. The countries such as United States, European Union, Japan, Canada etc. follow divergent legal pathways to avoid these conflicts. In this article, the patent dancing in US and patent linkage systems in various countries are elaborated. As for India, few generic manufacturers attempted to resolve patent disputes through lawsuits, yet no patent linkage system is established by legislation.

Keywords: Biosimilar, Biologics, Reference Product Sponsor (RPS), Abbreviated Biologic Licence Application (aBLA), Patent Dance, Patent Linkage, United States Food and Drug Administration (USFDA)

The discovery and development of two major categories of drugs, small molecules and biologics play a key role in extending the life of patients with awful diseases such as cancer. Small molecules are the drugs manufactured from chemical substances whereas, biologics are protein based complex molecules obtained from living sources. Until 1990, the pharma companies are much involved in manufacturing small molecules, and they occupied a predominant position in pharmaceutical market in United States of America in comparison with biologics. As several different methodologies can be adopted to obtain identical compounds in the case of small molecules and also the enactment of Hatch-Waxman Act (1984), the percentage entry of small molecule 'generics' in the market was increased from 35% to 85%.[1-5] This is echoed in moderate drug price and more accessibility of drugs to patients. In contrast, the complexity of the structure and folding of amino acid chains in biologics, even a small difference in manufacturing process causes deviations in the structure of active ingredients in follow on products. Due to the difficulty in producing similar biologics and the patent disputes between the manufacturers of innovator drug and the biosimilar, the growth of 'biogeneric' counterparts of branded drugs get hindered. These issues raise the cost of biologics and make part of patient population unaffordable to buy these potential drugs.[6-14]

†Corresponding author: Email: priyarega-che@saranathan.ac.in

Patent Dancing in US

According to the Hatch-Waxman Act, all the patents obtained for reference product must be listed in orange book except manufacturing process patents. Since identical versions of small molecules with low molecular mass can be achieved in several routes even if the information on process patents is not known, as opposed to complex biologics where process patent is vital. Since this existing Act cannot be used to resolve patent disputes prior to the approval and marketing of biosimilar drug by United States Food and Drug Administration (USFDA) to bring down the exorbitant price of biologics, US Congress enacted the Biologic Price Competition and Innovation Act (BPCIA) in 2009. The BPCIA provides a framework called 'patent dance' for facilitating patent litigation between Reference Product Sponsor (RPS) and Biosimilar Applicant (BA) prior to the marketing of 'biogenerics' and also created an abbreviated approval pathway for biosimilar product. After the completion of manufacturing and testing process of biosimilar, BA files 351(k) abbreviated Biologic Licence Application (aBLA) to FDA. While review process is in progress, both RPS and BA are required to engage in exchanging information on their products to initiate first phase of litigation. The schematic representation of the steps in patent dancing is given in Fig. 1.

In the first step of patent dancing, BA should send a copy of aBLA to RPS and provide the information on manufacturing methodologies of biosimilar within

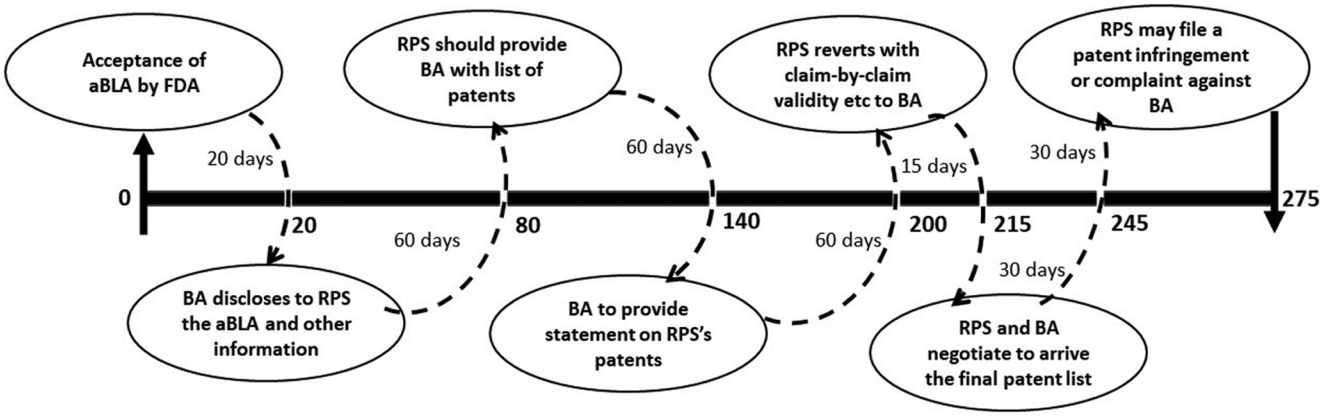

Fig. 1 — Steps and timelines in patent dancing

20 days of submitting application to FDA. The time period of 60 days is given to RPS to issue a list of patents that are believed to be potentially infringed by BA. They can also provide a list of patents for which sponsor is willing to offer licence. Then within 60 days of receiving infringed patent list from RPS, BA should respond with a detailed explanation asserting the invalidity, unenforceability and non-infringement of patents filed by sponsor.

Sponsor can take another 60 days of time to provide detailed statement asserting the validity and enforcement of their product. They can also give their own contentions on the infringement of patents that are already identified. After the exchange of information, both the parties negotiate among themselves and arrive at an agreement on the number of patents to be litigated immediately in the first phase of litigation. Patent dancing comes to an end by filing a complaint by RPS within 30 days of agreement, and litigation starts. If the parties do not reach agreement on negotiation, BA should provide the list of patents that it believed to be litigated. The number of patents mentioned by BA should not be exceeded by the number of patents by RPS. If BA does not want to list the patents, RPS should mention only one patent. Then, immediately parties exchange their information, and initial phase of litigation starts. After the initial phase of litigation, BA must provide pre-market notice at least 180 days before the launch of biosimilar in the market and triggers the second phase of litigation in which the patents that were not litigated in the first phase and also the new patents (not in the list of identified patents during the first phase of litigation) can be argued.[15-20]

However, BPCIA states that it is not mandatory for both the parties to engage in patent dancing for the market entry of similar biologics. In US, seven years after the enactment of BPCIA, the number of biosimilar suits filed in 2017 increased to 11 from 6 in the previous year, and this trend is continued in the following years. The increase in biosimilar litigation is due to the impact of the decisions made by the Supreme Court and the Court of Federal Circuit on expedition of aBLA process. If a biosimilar applicant does not engage in the initial information exchange, the reference product sponsor can file a declaratory judgment (DJ) suit. This DJ has the potential to speed up first litigation phase by eliminating nearly 250 days of negotiations between the sponsor and the biosimilar applicant. For instance, in a dispute between Amgen (RPS) and Sandoz (BA) in 2014, concerning Sandoz's Zarxio product, a biosimilar to Amgen's Neupogen, Sandoz decided not to engage in patent dance and disclosed neither its aBLA nor the manufacturing information about the product, but it sent 180 days pre-notice of launching its product. Amgen went to court to seek an injunction to force Sandoz to dance. In 2017, US Supreme Court held that Amgen could not force Sandoz to participate in the dance and that its only remedy was to file a declaratory judgment action.

Another pathway to lessen the prosecution time is to collapse two phase litigation into single phase by providing 180 days pre-notice along with aBLA application. Even though there are number of possibilities to expedite the legal proceedings, BA always does not choose to opt out of dancing. In contrast to the previous case between Amgen and Sandoz, the suit concerning Sandoz's biosimilar pegfilgrastim under the brand name Neulasta, Sandoz chose to engage in patent dancing and provided Amgen with a notice of commercial marketing of its product.

One year later, Amgen filed a filgrastim suit on infringement of the same patents (antibody purification patent and method of treatment patent) as in the case of pegfilgrastim suit. The court consolidated both the cases and gave final verdict in favour of Sandoz. The companies involved in disputes, change their attitudes based on their role either as sponsor or as applicant. For instance, in *Amgen* v *Genentech* case, Amgen initially exchanged information about its biosimilar with Genentech and also participated in subsequent steps in the patent dancing. However, as both the parties did not reach an agreement during negotiation, Amgen refused to provide a list of patents to be litigated. This is contrary to Amgen's former suit of forcing the biosimilar applicant Sandoz to take part in patent dancing.

After the US Supreme court judgement of first BPCIA suit (*Sandoz* v *Amgen* case, 2017), the biosimilar manufacturers are not willing to take part in the time-consuming patent dance and they involved in challenging the patents of sponsor directly through Patent Trial and Appeal Board (PTAB) of United States Patent and Trademark Office (USPTO). According to America Invents Act, 2011 (AIA), any accused infringer or the manufacturers who are anticipating infringement suit can challenge the validity of innovator company's patents at USPTO. The USPTO offers a host of administrative proceedings for challenging patent validity. These proceedings are called as "post-grant" proceedings which include *Inter Parties* Reviews (IPR) (*inter parties* - the patent challenger and the patent owner are directly involved in the proceedings as adverse parties) and Post Grant Reviews (PGR). IPR and PGR are like litigation in that the parties file briefs, depose witnesses and argue in front of three-membered panel of judges. But unlike federal court patent litigation, the proceedings concern only the validity of the challenged patent and do not concern infringement, damages or injunctions. As the proceedings are more compact and less time consuming (18 months), biosimilar makers have turned away from the patent dance and towards the PTAB. Since from the enactment of BPCIA (2010), there have been about 45 Federal Court litigations filed between sponsors and applicants involving biologics patents. At the same time, biosimilar makers have filed about 120 *IPR* petitions challenging biologics patents.

In June 2021, the updated report was published by USPTO on AIA trials involving challenges to biologic patents from 2012 to 2021. It clearly indicates that the number of *IPR* petitions aimed at biologics patents was growing from 8 petitions filed in FY2020 to at least 23 in FY2021. This significant rise in biologic patent challenges in 2021 compared to filings from 2017 to 2020 shows that the new strategy supports biosimilar makers to clear out biologic patents standing in the way of FDA approval.[21, 22]

Patent Linkage in EU and other Countries

In general, patent dispute between BA and RPS arises if there is no linkage between the patent expiration of brand name drug and the approval of biosimilar in the market. Many biosimilar products got tangled up due to patent infringement litigation even after its launch in the market. To resolve this issue, proper patent linkage system (certain linkage between the status of drug-related patent rights and the approval of a generic drug/biosimilar by the regulatory authority) should be established.

In EU, European Patent Office (EPO), a single forum through which inventors in all the 38 contracting states can protect their invention *via* a national patent or a European patent, and the biosimilar manufacturer can challenge RPS's key patents through EPO rather than multiple national patent courts. The EPO examines applications for European patents centrally, saving inventors the costs of parallel applications, while ensuring a high quality of granted patents. However, the validation and maintenance of granted European patents must be individually done in each country where they take effect. This can be a complex and potentially very costly process: validation requirements differ among countries and can lead to high direct and indirect costs, including translation costs, validation fees *etc*. These costs can be considerable and depend on the number of countries where the patent proprietor wishes to validate the European patent. To remove the complex and costly national validation procedures in EU, Unified Patent Court (UPC) and Unitary Patent (UP), a single patent with a unitary effect for all contracting states was proposed and recently established. This will strengthen the existing centralised European patent granting system and offer a cost-effective option for patent protection and dispute settlement across Europe.[23]

In Japan, The Ministry of Health, Labour and Welfare (MHLW) or the Pharmaceutical and Medical Devices Agency (PMDA) provides approval for the biosimilar only if it does not find any infringement of

product or usage patents. If the innovator companies want to complain about their patents, they need to negotiate with biosimilar manufacturers before drug price listing by the National Health Insurance (NHI). Otherwise, patent infringement litigation is initiated at the drug price listing stage or, in most cases, after the commercial launch of biosimilar.[24, 25]

Canada's regulatory medicines counterpart, Health Canada issued a guidance in 2010 for regulating biosimilars as Subsequent Entry Biologics (SEB). It created a unique system called Notice of Compliance regulations (NOC) which requires biosimilar companies to establish patent freedom-to-operate as a precondition for the issue of the NOC. According to NOC regulations, the innovator has the chance to list its relevant patents on the Health Canada Patent Register. The BA must submit freedom to operate with respect to the patents in patent register along with the submission of SEB application, and finally the invalidity, non-infringement and expiry of patents must be justified. If the patent owner and biosimilar manufacturer disagree about freedom to operate, a court case known as NOC proceeding will assess evidence about patent infringement and validity. The court will then decide whether to prohibit Health Canada from issuing the biosimilar a NOC because of the risk of patent infringement. No NOC can be issued while the court is considering the issues, which can take up to 2 years. If the biosimilar company wins, it gets its marketing authorization. If the biosimilar company loses, it has to wait until patent expiry to get its NOC. The biosimilar litigation landscape is complex because a conventional patent infringement or invalidity lawsuit may be initiated concurrently with, or after, a NOC proceeding.[25]

Patent Linkage in India

The patent system and the drug approval system exist as two separate and independent systems created under two different laws, and this poses a stumbling block in the market entry of biologics in India. Under Drug and Cosmetic Act (1940), Drug Controller General of India (DCGI) is responsible for approving any new innovator drug / generics / biogenerics in the market. Inventor company's reference product patents can be protected by The Patents Act (1970).[26,27] The communication between national drug regulatory authority of India, CDSCO and the Indian Patent Office makes the market entry of generics / biosimilars easy. Unlike US's orange book (small molecule generics) or patent dance (biologics), the patent linkage is not recognized in India by legislation. This was clarified by two different lawsuits filed in Delhi High Court in the years 2008 and 2009. The US based pharmaceutical company Bristol-Myers Squibb Co., sold its cancer drug Dasatinib in India under the brand name Sprycel, filed a lawsuit for preventing DCGI to grant marketing approval of generic drug manufactured by Hetero Drugs Ltd., India. The Court asserted that Drug controller's office has the sole responsibility to ensure whether the generic drug is not covered by valid patent before its approval. In another case, *Bayer* v *Cipla* and *Union of India*, the Court further clarified that no explicit legislation is passed through parliament for patent linkage in India.[28-30] The introduction of patent linkage is a policy decision to be taken by the law makers in the parliament. The other side of patent linkage is that in developing countries like India, the government is providing public health care. In order to keep it accessible and the most affordable, the government resists patent linkage.

Despite the absence of a patent linkage system, India is firmly establishing its global biopharmaceutical market through many initiatives and booming as a significant contributor in providing affordable similar biologics for patients affected with fatal diseases. It had approved its first biosimilar for Hepatitis B vaccine in the year 2000 and in the last two decades nearly hundred biosimilars were approved by Central Drug Standard Control Organisation (CDSCO), the drug regulatory authority of India. The cost of development of similar biologics in India is 90% less than that of European Union or United States which is attributed to the lower cost of labour and service fees, as well as less stringent regulatory approval criteria. The difference in the price of biosimilars in different countries is illustrated with transtuzumab (Herseptin) used in the treatment of breast cancer as an example (Table 1).[31]

Currently, several Indian biopharma industries are involved in developing a couple of hundreds of active

Table1 — Individual cost of transtuzumab in different countries

Country	Cost (US dollars)
USA	70,000
UK	41,247
France	39,629
Australia	44,146
Moracco	26,280
India	4,833

similar biologics and awaiting approval for market entry. The huge market potential and the interest by Indian pharma industry are not capitalized due to absence of a linkage system. While, Patent Linkage System is established in several countries to hasten the process of market access of biosimilars by reducing unnecessary patent infringement litigations, in India, the linkage system is yet to be established. The establishment of a patent linkage system in India is expected to provide an opportunity for the Indian manufacturers to dominate the biosimilar market owing to their potential manufacture at the most affordable price. This expectation has increased several folds in developing and under developed countries after India's success in the development and large-scale supply of COVID-19 vaccines during the pandemic. In this context, the authors feel that it is very relevant to quote a paragraph from an article published 15 years before and valid even today.[32,33]

"Patents remain by far the most controversial of the Intellectual property (IP) rights harmonized under Trade-Related Aspects of Intellectual Property Rights (TRIPS). Not only do patents confer significantly stronger rights of exclusivity than other IP regimes, the subject matter of patents-technology-most directly impinges on economic prosperity. In the case of pharmaceuticals, access to patented technology can literally become an issue of life or death. Indeed, LPA 443/2009 page 23 of 27 the recent showdown in the World Trade Organization (WTO) over compulsory licensing of AIDS medication served as a wake-up call for many who had previously dismissed patents as a technical domain of interest only to specialists. Patent protection suddenly became the ugly face of globalization, seemingly a hazard to public health and travesty of social justice. Discontent over TRIPS' patent provisions goes well beyond pharmaceuticals. Patent systems are, by nature, the most administratively demanding form of IP protection, requiring extensive record-keeping and sophisticated technical analysis. Yet, given that the top ten industrialized countries account for 94% of patents granted worldwide, the benefits of patent protection are heavily skewed. Even TRIPS' defenders concede that its patent mandate represents an onerous and costly obligation whose immediate benefits will redound primarily to rich multinational companies. Furthermore, because technology is a cumulative enterprise, TRIPS opponents worry that enforcing patent monopolies will deny developing countries access to vital technology, relegating them to a future of economic dependency."

References

1 Li Y, Does it still take two to tango? A modern interpretation of the BPCIA's patent dance? *Journal of Intellectual Property and Entertainment Law*, 9 (1) (2019) 107.

2 Boehm G, Yao L, Han L & Zheng, Development of the generic drug industry in the US after the Hatch Waxman Act of 1984, *Acta Pharmaceutica Sinica,* 3 (5) (2013) 297.

3 Roy A, The Competition Prescription: A Market-Based Plan for Affordable Drugs, FREOPP (2017). https://freopp.org/a-market-based-plan-for-affordable-prescriptiondrugs-931e31024e08.

4 Orphan Drugs Lead 2015 Approvals, *Biotech Primer* (2016). https://weekly.biotechprimer.com/orphan-drugs-drive-fda-approval-record-for-2015/

5 How do Drugs and Biologics Differ? *Biotechnology Innovation Organization*, https://www.bio.org/articles/how-do-drugs-and-biologics-differ.

6 Nikolov N P & Shapiro M A, An FDA perspective on the assessment of proposed biosimilar therapeutic proteins in rheumatology, *Nature Reviews Rheumatology,* 13 (2017) 123.

7 Lemery S J, Ricci M S, Keegan P, McKee A E & Pazdur R, FDA's approach to regulating biosimilars, *Clinical Cancer Research,* 23 (2017) 1882e5.

8 Levi E L, Using data exclusivity grants to incentivize cumulative innovation of biologics' manufacturing processes, *American University Law Reviews,* 66 (2017) 911.

9 Van de Vooren K, Curto A & Garattini L, Biosimilar versus generic drugs: Same but different? *Applied Health Economics and Health Policy*, 13 (2015) 125.

10 US Food and Drug Administration (USFDA), Guidance for industry: Scientific considerations in demonstrating biosimilarity to a reference product, U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2015). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product.

11 Halim L A, Brinks V, Jiskoot W, Romeijn S, Haselberg R & Burns C, Quality and batch-to-batch consistency of original and biosimilar epoetin products, *Journal of Pharmacetical Science,* 10 (2016) 542.

12 Chang L-C, The biosimilar pathway in the USA: An analysis of the innovator company and biosimilar company perspectives and beyond, *Journal of Food and Drug Analysis,* 27 (2019) 671.

13 Gayatri S, India to power the more widespread use of biosimilars, *Current Science*, 116 (9) (2019) 1451.

14 Gayatri S, Bio-business in brief: The debate over biosimilars, *Current Science*, 98 (12) (2010) 1575.

15 Sullivan T J, The patent dance, *European Biopharmaceutical Review*, Finnegan (2018).

16 Ladonnikov & Alexej, The biosimilar patent dance - If you don 't dance you ' re no friend of mine, *Santa Clara High Technology Law Journal*, 35 (1) (2018) 135.

17 Coggio B D, Biosimilars: "The patent dance" "I won't dance/don't ask me, *27th Annual Fordham IP Conference*, New York (2019).

18 Tanaka J, "Shall" we dance? Interpreting the BPCIA's Patent Provisions, *Berkeley Technology Law Journal,* 31 (2016) http://dx.doi.org/10.15779/Z383S0S.

19 Goodwin, Guide to the BPCIA's Biosimilars Patent Dance (2021).https://www.bigmoleculewatch.com/wp-ontent/uploads/sites/2/2021/11/Goodwin-Biosimilars-Patent-Dance-Guide-Nov-2021.pdf.

20 Priyarega S & Natarajan R, An overview of biosimilars for cancer, diabetes mellitus, rheumatoid arthritis and other immune-mediated diseases approved between 2016 and 2021, *Results in Chemistry*, 4 (2022) 100356.

21 Belt E P & Zacharakis M L, Wallflowers: Biosimilars don't dance – they go to the PTAB, McCarter & English, LLP (2021).

22 2021 PTAB Year in Review: Analysis & Trends: Biologics at the PTAB, Statistics and Insights into notable biologics decisions, https://www.jdsupra.com/legalnews/2021-ptab-year-in-review-analysis-1159061.

23 Malkin B J & Esq, Biosimilars patent litigation in the EU and the US: A comparative strategic overview, *GaBI Journal*, 4 (3) (2015) 113.

24 Masuda S, The trend in patent infringement litigation against generic drugs or biosimilars in Japan, *Journal of Generic Medicines*, 15 (1) (2019) 10.

25 Malkin B J & Esq, Biosimilars patent litigation in the EU and the US: A comparative strategic overview, *GaBI Journal*, 5 (2) (2016) 60.

26 Panda S, Singh P K, Mishra S, Mitra S, Pattnaik P, Adhikary S D & Mohapatra R K, Indian biosimilars and vaccines at crossroads–replicating the success of pharmagenerics, *Vaccines,*11 (2023) 110, https://doi.org/10.3390/vaccines1101011.

27 Patil N S, Patent linkage in FTAs and Indian position, *International Journal of Law Management & Humanities,* 4 (2) (2021) 73.

28 Mittal A, Patent linkage in India: Current scenario and need for deliberation, *Journal of Intellectual Property Rights*, 15 (2010) 187.

29 Singh M & Gupta S, India: Patent Linkage and Indian Laws (2019). https://www.mondaq.com/india/patent/871208/patent-linkage-and-indian-law.

30 Singh M, How to deal with patent dancing? (2020) https://www.lexology.com/library/detail.aspx?g=007d60dd-a4d8-46b9-bffd-e64512e9b850.

31 Boutayeb S, Boutayeb A, Ahbeddoul N, Boutayeb W, Ismail E, Tazi M & Errihani H, Estimation of the cost of treatment by chemotherapy for early breast cancer in Morocco, *Cost Effectiveness and Resource Allocation,* 8 (1) (2010).

32 Pager S A, Patents on a shoestring: Making patent protection work for developing countries, *Georgia State University Law Review*, 23 (2007) 755.

33 Gupta N, Verma R K, Gupta S & Prinja S, Cost Effectiveness of trastuzumab for management of breast cancer in India, *JCO Global Oncol*ogy, 6 (2020).