

Exclusivity Protections for Biopharmaceuticals

Protection of intellectual property (IP) rights continues to act as a key aspect of the legislative mechanisms for the licensure of generic drugs and biosimilars. IP rights are crucial for business survival in stringently regulated pharmaceutical markets.

Innovator IP rights are protected in order to incentivise continuing investment in the discovery of new medicines. The protection is centred on the twin pillars of patent protection and regulatory exclusivity for first-entrant reference products. Conversely, enabling timely approval of generics and biosimilars maximises price competition and lowers the cost of life-saving medicines. This is achieved through abbreviated nonclinical and clinical testing of generics and, to some extent, biosimilars.

In the EU, marketing approval of similar medicinal products without full clinical testing was first established by the European Economic Community (EEC) through the Council Directive 65/65/EEC of 26 January 1965. The EU framework has evolved over the years through amendments to this directive and enactment of other pieces of legislation at the member state (MS) and EU levels. In the US, the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) added Section 505(j) to the Federal Food, Drug and Cosmetic Act (FDCA) establishing the abbreviated new drug application (ANDA) pathway for the approval of generic drugs. Hatch-Waxman made it possible to challenge 'invalid' or 'unenforceable' reference-product patents while enabling restoration of innovator patent term lost to lengthy approval and development processes (1).

Approval Pathways for Generics and Biosimilars

The basic technical requirements for the approval of small molecule generic medicines are essentially identical in all advanced pharmaceutical markets. They

include requirements pertaining to current good manufacturing practices (cGMP), documentation of *in vivo* bioavailability and bioequivalence (BA/BE), as well as pharmacokinetic (PK) study design and statistical analysis approaches. Due to the molecular and biochemical complexity of biological products, however, assessment of BA/BE alone is insufficient to demonstrate biosimilarity, much less sameness, between the reference biologic and a biosimilar. At a minimum, some toxicological and clinical efficacy and safety testing (including immunogenicity) is required in order to demonstrate biosimilarity. Consequently, regulatory requirements for biosimilarity are commensurately intricate and have taken longer to evolve. The EU pioneered the establishment of standards for approval of biosimilars with European Commission (EC) Directive 2001/83/EC and ensuing amendments and guidelines, which led to the first approval of a biosimilar in the EU in 2006. In the US, enactment of the Biologics Price Competition and Innovation (BPCI) Act of 2009 (the 'Biosimilars Act') established a pathway for FDA approval of biosimilars under the Public Health Service Act Section 351(k). Many unresolved questions remain about FDA's implementation of key BPCI Act provisions, including on patent and exclusivity protections. Notwithstanding this uncertainty, biopharmaceutical companies are already pursuing biosimilar development programmes that include the US as a major target market.

Innovation versus Competition

For both innovator and generic or biosimilar companies alike, there is an imperative to understand the regulatory

forces influencing the delicate balance between sustainable innovation and price competition. By some estimates, it takes 10 to 15 years of R&D to develop a single medicinal product through to licensure at an estimated cost of \$1.2 billion (2). Since the lifespan of a nonprovisional patent is 20 years from the date of filing, the time expended in R&D and regulatory approval reduces effective patent term by 50 to 75 per cent. Although a pharmaceutical product may be protected by numerous patents filed at different junctures of the product development continuum – in some cases for 'evergreening' objectives – the most important patents for regulatory purposes are those that cover the composition of matter (COM), manufacturing technology, and/or intended method of use (3). Good patent management entails, among other considerations, having a sound strategy for maximising effective patent life. The competitive dynamics for biosimilars differ markedly from generic drugs, however, starting with higher developmental costs for biosimilars. Secondly, EU experience shows that market penetration is slower for biosimilars, in part due to lack of automatic substitution at the pharmacy level. In the US, for example, the regulatory standard for 'interchangeability' is more stringent than for biosimilarity.

Patent and Regulatory Exclusivity

Whereas patent exclusivity provides the right to exclude others from exploiting the invention during the patent term, regulatory exclusivity grants marketing rights over a finite period following regulatory approval; patent and regulatory exclusivity may run concurrently. The concept of patent term restoration for innovator products arose

Onesmo Mpanju,
Stephen Dodds and
Henrietta Ukwu of PPD, Inc

as a legislative fix for loss of patent life due to regulatory approval processes. The US and EU approaches to exclusivity protection are similar in many respects, but differ in some significant ways.

Patent Protection for Small Molecule Drugs

Despite the existence of the European Patent Office (EPO) there are, as yet, no EU-wide patents. Patenting of pharmaceutical research inventions is regulated at MS level. Supplementary protection certificates (SPCs) are used by the EU to manage disparities among MS patenting systems. Different EU countries may grant patent term extension via SPCs, but the length of extension is determined nationally. Previously, infringement claims related to the testing of a generic drug before patent expiry of the reference product were regulated by individual countries via 'experimental use exemption' laws. These provisions varied significantly across the EU creating a complex patent-dispute resolution environment. EU law under Directive 2001/83/EC, as amended by Directive 2004/27/EC, provides for an exception to patent infringement at the EU level to enable the conduct of product development studies necessary for obtaining marketing authorisation for generic drugs. The testing safe-harbour period (similar to the US 'Bolar exemption'(4)) is described in Article 10(6) of Directive 2004/27/EC. Patent rights are enforceable by the owner and any declarations regarding their status are not part of the submission dossier and do not affect acceptability for filing by the competent authorities.

In the US, patent information for FDA regulated drugs is published in the *Orange Book* (Approved Drug Products with Therapeutic Equivalence Evaluations). The *Orange Book* facilitates resolution of patent disputes between innovator and generic manufacturers. A generic applicant must certify to FDA that filing of an ANDA does not infringe upon patent claims of the reference product. FDCA lists four types (or paragraphs) of such patent certifications, namely:

- Paragraph I – patent information on the innovator drug has not been filed

- Paragraph II – original patent has expired
- Paragraph III – patent is about to expire and generic will not enter market until it does
- Paragraph IV – patent is invalid or will not be infringed by the manufacture, use or sale of the generic drug

If filing Paragraph IV certification, the generic applicant must also notify the holder of the original new drug application (NDA) regarding the same. The original licensee has 45 days to initiate a patent infringement suit against the ANDA applicant, following which the FDA is barred from approving the ANDA for 30 months (so called '30-month stay') unless the suit is resolved earlier in favour of the generic applicant.

Under Hatch-Waxman, mere submission of an ANDA (with Paragraph IV certification) may construe an act of infringement subject to injunctive relief until expiration of the innovator's patent. The Hatch-Waxman patent-dispute resolution framework presumes that generic manufacturers are 'judgment proof' with regard to infringement action since generic drug profits are substantially less compared to the financial loss suffered by the innovator upon introduction of a competing generic. Pre-approval dispute resolution, therefore, guards against *de facto* erosion of innovator IP rights while incentivising legal challenges to questionable patents. For example, first entrant generics qualify for 180-day generic drug exclusivity.

Patent Protection for Innovator Biologics

In the EU, the Bolar-like exemption for pre-approval testing described above for drugs also applies to biosimilars. In the US, the BPCI Act provides for the exchange of confidential information – including patent claims – between a biosimilar applicant and the reference product innovator when submitting a biosimilar licensing application to FDA. This process is summarised in Figure 1.

The trigger event for the patent dispute resolution process is the filing of a Section 351(k) biosimilar application. The FDA has not issued guidelines regarding

implementation of these provisions. Since no biosimilar has gone through the Section 351(k) pathway, it remains to be seen whether applicants will share with reference product competitors manufacturing and other confidential information per BPCI Act. There is evidence that some biosimilar developers will opt to pursue full biologics license applications (BLAs) instead. Other stakeholders have expressed their concerns regarding the potential for anti-competitive collusion among innovator and biosimilar companies as a consequence of the BPCI Act patent resolution scheme. These and other issues remain murky until FDA promulgates regulations and issues guidelines on biosimilars.

Regulatory Exclusivity for Small Molecule Drugs

In the European Economic Area (EEA) (EU plus Norway, Iceland and Liechtenstein) under Directive 65/65/EC, as amended, innovator products submitted as full dossiers are entitled to 10 years of data exclusivity, unless a particular MS has elected to operate six years of data exclusivity. These data exclusivity provisions apply from the date of first approval in an EU MS and are applicable to all products submitted on or before 31 October 2005. However, medicinal products submitted on or before 19 November 2005 using the centralised procedure are entitled to 10 years of data exclusivity in all EEA countries. EU pharmaceutical legislation per revised Directive 2001/83/EC, as last amended by Directive 2004/24/EC and 2004/27/EC, redefines the regulatory exclusivity for all medicinal products approved in the EEA via the Decentralised Procedure (DCP), Mutual Recognition Procedure (MRP), and National Procedure (NP). Regulation (EC) No 726/2004 redefines the regulatory exclusivity for all medicinal products approved in the EEA via the Centralised Procedure (CP). The Directive and Regulation define the same exclusivity period irrespective of the approval procedure used to gain MA for a medicinal product in the EEA.

All marketing authorisation applications (MAAs) for medicinal products submitted for approval after 1 November 2005 via DCP, MRP or NP, and after 20 November

2005 via CP, under Article 8(3) of 2001/83/EC – the so-called ‘full’ dossiers – are entitled to eight years of data exclusivity as well as a consecutive two years of marketing exclusivity from the date of initial authorisation in the EEA. Thus, there is a total of 10 years of marketing exclusivity from the date of initial authorisation. All of this makes for a complex picture in the EEA as products submitted before 31 October 2005 via NP and MRP will lose their data exclusivity in the ‘six-year’ countries in 2012, but in the countries in the 10-year bracket the data exclusivity will remain in place until 2016. The 2016 expiry of data exclusivity is also applicable to products approved via the CP submitted before 19 November 2005. Conversely, the first products submitted under the revised directive and regulation will lose data exclusivity in 2014, though generics and biosimilars referencing these innovators cannot be launched until 2016.

In the US, patent term restoration is calculated on the basis of the regulatory review period, comprising of the sum of the clinical trial period and FDA review

time (limited to five years), reduced by a period of lack of due diligence on the part of the innovator, half of the time in clinical trials, and the period that would extend the effective patent life beyond 14 years. Only one extension is allowed per regulatory review period. Longer exclusivity terms and/or extension of exclusivity may be granted for some NCEs, as well as products with orphan drug status designation (seven years exclusivity from first approval) and paediatric exclusivity (six months add-on to existing exclusivity).

Regulatory Exclusivity for Biosimilars

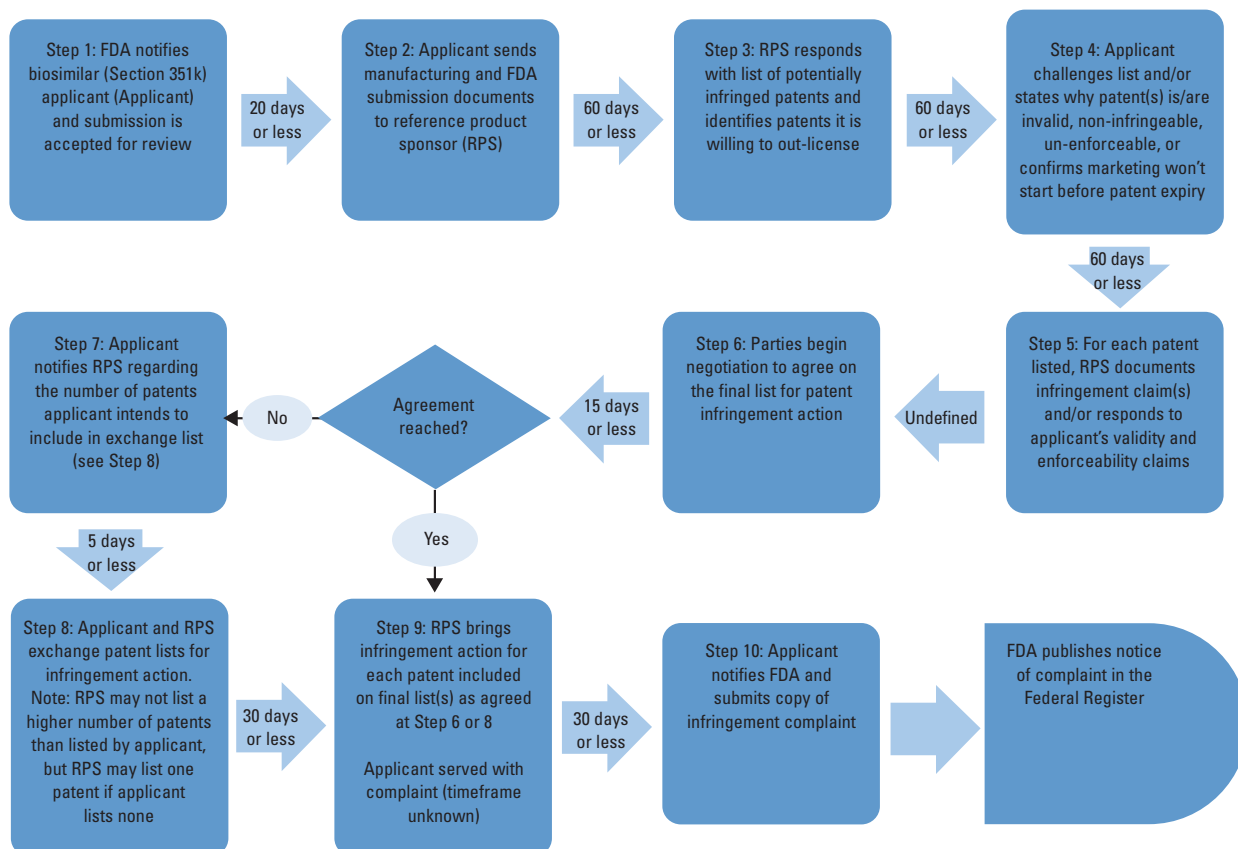
In the EEA, both small and large molecule products receive a 10-year regulatory exclusivity period as described above for small molecules (with the caveats of MS differences). In the US, the BPCI Act grants a 12-year exclusivity period to the reference biological product, which the FDA previously characterised as ‘marketing’ exclusivity (5). The BPCI Act prohibits the FDA from approving a biosimilar (or interchangeable) product

before 12 years have elapsed from the date the reference biologic was approved. The legislation creates a safe harbour, free testing period during which filing of a biosimilar application to FDA is permitted after four years from the date of licensure of the reference biologic. This compares to a one-year safe harbour period under Hatch-Waxman for filing of a new drug application under FDCA Section 505(b)(2) or ANDA with Paragraph IV patent certification.

Safe harbour provisions prevent unintended lengthening of exclusivity by allowing sufficient time for biosimilar or generic product testing and regulatory submission. Arguably, market exclusivity creates a higher barrier to market entry compared to data exclusivity in that it disallows a generic or biosimilar product developer from legally launching their product. In contrast, data exclusivity prohibits a regulatory authority from approving a generic or biosimilar using a previous finding of safety and efficacy of an innovator product. During the data exclusivity period, the generic or

Figure 1: BPCI Act patent resolution process

Source: Adapted from Patent Provisions of BPCI Act (HR3590-686)



biosimilar developer can perform their own development and clinical testing under regulatory oversight and submit the data for review and approval upon expiration of marketing exclusivity. The question of whether the BPCI Act intended to grant innovators with marketing rather than data exclusivity has taken added significance following the emergence of competing proposals in the US Senate mirroring innovator versus biosimilar viewpoints. Further, the current US administration has proposed in the 2012 budget to lower the exclusivity period for biosimilars from 12 to seven years. It is not known whether the seven years will be data or marketing exclusivity.

Conclusion

Although the EEA position on exclusivity term for NCEs and biologics approved with a full dossier is generally clear, the picture is less so when the differences between 10-year and six-year member states are considered. The US position on exclusivity for biosimilars is still unsettled. Although the original exclusivity period in BPCI Act was set at 12 years and the FDA interpreted the provision as intending to grant marketing exclusivity, recent developments have challenged this interpretation. Additionally, there are ongoing legislative initiatives to lower the exclusivity period to seven years. The exclusivity periods for NCEs are well defined in both the EU and US – namely 10 or five years respectively. Previously, exclusivity-term differences between the two markets did not figure prominently in generic development strategy because for one thing most developers were regionally focused. However, the emergence of truly global generic players may alter this dynamic in the future. There is an increasing need for generic developers to pursue multi-national product development strategies that should take into consideration differences in exclusivity terms among various regional markets.

Lastly, for biosimilars in particular, the choice of an optimal development and regulatory strategy will depend on an objective assessment of product and indication-specific testing requirements and prevailing patent and exclusivity protections in various markets. All of these factors impact the business case.

Contrary to old paradigms, however, innovation and competition will not always prove mutually exclusive as the dichotomous juxtaposition of first entrant biologic versus biosimilar is slowly blurred by the emergence of ‘biobetters’ and ‘biosuperiors’. These terms, although currently without statutory import, encapsulate biopharmaceutical pathways for improving upon the safety, efficacy and COM of existing biological products without playing regulatory second fiddle.

References

1. Higgins MJ and Graham SJ, Balancing Innovation and Access: Patent Challenges Tip the Scales, *Science* 326: pp370-371, 2009
2. Knowles SM, Fixing the Legal Framework for Pharmaceutical Research, *Science* 327: pp1,083-1,084, 2010
3. Huml RA and Baum AR, Key Aspects of Pharmaceutical Due Diligence Intellectual Property Assessment – Part I, *Regulatory Focus* 15(10): pp28-33
4. Refers to Roche v Bolar in which the US Court of Appeal ruled that experimental use of a patented drug in research for the purpose of gathering data for eventual ANDA filing qualified as patent infringement. Congress subsequently enacted an exemption to Bolar (hence, ‘Bolar’ exemption) allowing for use of reference products experimentally without infringing
5. Docket No FDA-2010-N-0477, Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, *Federal Register* 75(192): pp61,497-61,501, 5 October 2010

About the authors



Onesmo Mpanju is Associate Director of Regulatory Affairs at PPD, Inc. He has more than nine years of regulatory experience and manages regulatory submission projects for many of PPD’s commercial clients. In addition, Onesmo advises PPD’s noncommercial clients, such as governments and public health organisations, on key regulatory matters. Prior to joining PPD, Onesmo worked as a review scientist at the US FDA. Onesmo obtained his PhD from the University of British Columbia in Canada, in 2001, and has authored and co-authored several publications and scientific presentations on the molecular biology of retroviruses and filoviruses. Email: onesmo.mpanju@ppdi.com



Stephen Dodds is Technical Manager of Regulatory Affairs Development at PPD, Inc and has more than 15 years of regulatory experience. He is experienced in working with the regulatory and legislative framework to gain approval of clinical trial applications in countries around the world. Stephen’s current responsibilities include managing regulatory submission projects and providing regulatory strategy and training within PPD. In addition, he provides general advice and training to other regulatory affairs professionals and outside consultants. Stephen has a BSc in Applied Biology and a diploma in business studies from the University of Hertfordshire in the UK. Email: stephen.dodds@ppdi.com



Henrietta Ukwu is Senior Vice President of Global Regulatory Affairs at PPD, Inc, overseeing the company’s global regulatory activities and providing clinical vaccine expertise to support the company’s vaccine and biologics business growth objectives. Prior to joining PPD, she has served as the Vice President of Global Regulatory Affairs for Pfizer, Wyeth Pharmaceuticals and Merck. Henrietta is an internist and infectious diseases physician with more than 18 years of pharmaceutical industry experience. She has overseen the development of many products and approval of 14 new products. She is a fellow of the American College of Physicians and the Regulatory Affairs Professional Society. Email: henrietta.ukwu@ppdi.com