

# The battle over global drug markets: enforcement of pharmaceutical patents in the United States, Europe and Japan

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Discovery consists in seeing what everyone else has seen, but understanding it for the first time.

Albert Szent-Gyorgyi,  
*Nobel laureate in physiology or medicine*

The pharmaceutical industry is one of the most productive and competitive industries in the world. Many of the large pharmaceutical companies (often termed 'Big Pharma') base their primary operations in the USA and maintain extensive facilities in countries around the world. Pharmaceutical research is, therefore, an activity of global importance. The intensely competitive and global nature of Big Pharma, and the pharmaceutical industry in general, make pharmaceutical product innovation and development a crucial determinant of any company's success.

Innovator pharmaceutical companies are constantly challenged by the time and cost required to bring new, branded drug products, ie the so-called 'pioneer' drugs, successfully to market.<sup>1</sup> Companies must continually seek new and improved ways to expedite the research, development, and regulatory approval phases of drug development and to manage competition from generic drug manufacturers. These companies seek to maintain an advantage in the marketplace both by introducing new drug products whenever possible and by finding new ways of protecting existing drug products, widening the breadth of patent protection for innovative products. Successful companies have maintained a competitive advantage in the global pharmaceutical industry by evaluating and strengthening the way existing drug products are protected, frequently changing the nature of protection under the patent laws by improving upon the product itself.

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<sup>1</sup> Despite billions of dollars of investment annually in research and development, the number of pioneer drugs coming to the market in

## Key issues

- Recent court decisions on the invalidity or non-infringement of pharmaceutical patents reflect the vulnerabilities of these patents in protecting later stage or second generation drug products that provide improvements over earlier formulations.
- Parties seeking to bring generic pharmaceutical products to market are becoming increasingly aggressive at commencing suit against pharmaceutical companies on second generation patents. Patent litigators and prosecutors must be aware of the evolving case law on issues of novelty/anticipation, obviousness/inventive step, and the obstacles to proving infringement.
- This article reviews the strategic options available for pharmaceutical companies to globally manage the life cycle of their patentable assets in view of the evolving case law.

In the pharmaceutical industry, there are several types of patents an innovator can obtain. The main type of patent is directed to brand-name pioneer drugs and their uses, eg for specific indications. Pioneer drug patents include (i) product patents that cover the active ingredient or compound in a drug; (ii) process patents that cover a process for manufacturing a drug; (iii) method-of-use patents that relate to a particular method of using a drug; and (iv) formulation patents that cover both the active and inactive ingredients in a drug (eg a final dosage form, tablet, or capsule).<sup>2</sup> These types of patents are infringed by the sale and use

recent years has been declining: J Whalen, 'Glaxo Becomes Master of Reinventing Drugs', *Wall Street Journal*, 17 April 2008.

<sup>2</sup> D Bassan, 'In Cipro We Trust: But How Do We Feel About Our Drug Patent Laws?', in PB Hutt (ed.), *Food and Drug Law: an Electronic Book of Student Papers* (2002), <http://leda.law.harvard.edu/leda/data/496/Bassan.html>.

of the pioneer drug product itself, the way it is made and used and the dosage form in which it is sold.

Beyond the brand name pioneer drug product, secondary or 'second generation' drug products are regularly developed to provide improved effectiveness, safety, and ease of use for the patient. The patents underlying those second generation products provide valuable intangible assets for the innovator pharmaceutical company. Successful pharmaceutical firms have strategically harnessed the ongoing nature of scientific discovery by patenting their inventions in stages, to acquire successive layers or generations of patent protection for their products.

In order to have value, however, second generation patents must provide effective economic benefit. Today for Big Pharma, that benefit is affected by the US patent system and increasingly by patent systems elsewhere. The degree to which pharmaceutical companies can capitalize upon the value of their second generation patents to extend the protection given to existing drug products depends, in part, on the national patent landscape and also on the regulatory landscape for generic drug products and their entry into the marketplace. This paper examines the patent laws, drug approval regulations, and court decisions for securing and enforcing later-stage or second generation pharmaceutical patents in three major jurisdictions: the USA, Europe/UK, and Japan.<sup>3</sup> This assessment provides an instructive insight on the changing terrain of drug approval and the commercial market for both generic and innovator drug companies.

Part I gives an overview of the legal basis for second generation pharmaceutical patents under the Patent Laws of the United States.<sup>4</sup> It also considers the most recent decisions of the Supreme Court and the Federal Circuit Court of Appeals. These decisions reflect the vulnerabilities of the hotly contested second generation drug patents in the USA, both in terms of validity and enforcement.

Part II examines the law on the validity and enforcement of second generation pharmaceutical patents in Europe. Because the determination of infringement (and in some countries validity) of a European patent is governed by the domestic law of the country in which enforcement is carried out, the focus in this

paper will be placed on UK court rulings. The UK is one of the more influential jurisdictions in the European Union. Contrasts will be drawn between the standard of enforcement in UK courts and the standard of validity in the EPO.

Part III examines second generation pharmaceutical patents in Japan, with a focus on the most recent positions that the Japanese Supreme Court has taken with regard to the proper judicial treatment of their scope of enforcement. The paper concludes by reflecting upon the strategic options available for pharmaceutical companies to manage the life cycle of their patentable assets globally.

## Part I: The United States

In the pharmaceutical context, the delicate balance of the patent system allows pharmaceutical companies to rely on a number of years of competition-free sales of their patented drug products. During this time, the innovator companies can independently set pricing structures to recoup their very high development costs, to reward their stockholders, and to invest in future drug development. When pharmaceutical patent protection expires, society benefits from generic drug companies entering the market and engaging in intense competition with innovator companies to lower drug prices.

The enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the 'Hatch-Waxman Act')<sup>5</sup> attempted to strike a balance between what seemed to be irreconcilable competing interests of the innovator and the generic pharmaceutical companies. The Hatch-Waxman Act endeavoured to facilitate the Food and Drug Administration's ('FDA') approval of generic drugs and their entry into the market while balancing the incentives for continued investment in new and innovative drug products.<sup>6</sup>

To effect the first goal, Hatch-Waxman provided for, *inter alia*, the filing of an Abbreviated New Drug Application ('ANDA') that allows a generic drug maker to piggyback on the innovator drug maker's approval and safety and efficacy data, as long as the generic proves its drug's bioequivalence to that of the innovator drug.<sup>7</sup> To effect the second goal, Hatch-Waxman restored at

3 'European' jurisdiction is still a fond hope. Currently, patents are enforced nationally although they can be opposed, for a period of time, centrally in the European Patent Office ('EPO'). Thus, this paper addresses UK decisions as a European component.

4 Patent Act 1952, ch. 950, 66 Stat. 792 (codified at 35 USC).

5 Pub. Law No. 98-417, 98 Stat. 1585 (1984) (codified at 21 USC §355, 360cc, and 35 USC §§156, 271).

6 149 Cong. Rec. S15582, S15584 (25 November 2003) (remarks of Sen. Kennedy, Medicare Prescription Drug, Improvement, and Modernization Act 2003).

7 Bioequivalence is achieved if the rate and extent of absorption of the generic drug's active ingredient are shown not to bear significant differences from the innovator's drug: 21 USC §355(j)(8)(B).

least a part of the patent term for pioneer drugs that had undergone protracted pre-market testing to ensure drug safety and efficacy as mandated by the FDA, after the patent had been issued. Under these provisions, branded drugs have been entitled to an average extension of about 3 years in patent term. This extension allows the patent owner more time to recoup the expenses of drug development and to fund subsequent research on new drugs by marketing the drugs at patent-protected prices.<sup>8</sup>

Hatch-Waxman also provided a mechanism for litigating issues of infringement and validity of patents covering innovator drugs before the generic enters the market. The Hatch-Waxman procedure is complex, but is essentially as follows: the innovator drug maker identifies and the FDA lists any patents claiming the drug or methods of using it in the 'Approved Drug Products With Therapeutic Equivalence Evaluations', known as the Orange Book.<sup>9</sup> ANDA applicants wishing to enter the market before expiration of these patents must include in the ANDA an application for approval to market and a 'Paragraph IV certification' that the listed patent(s) are invalid or not infringed by the manufacture, use, sale, or offer for sale of the generic equivalent, and must notify the patent holder of the certification.<sup>10</sup> Hatch-Waxman created subject matter jurisdiction where none existed before, such that the mere filing of an ANDA for a patented drug or its use is an act of constructive infringement, whereas the research and development needed for the ANDA filing is exempt from patent infringement.<sup>11</sup> If the patent owner files an infringement suit against an ANDA applicant within 45 days of receiving notice of a Paragraph IV certification, the FDA must stay approval of the ANDA for 30 months, or as otherwise ordered by the Court, to permit resolution of the lawsuit.<sup>12</sup>

Unsurprisingly, since its inception, the Hatch-Waxman Act has been at the epicentre of patent litigation between pharmaceutical innovators and generic drug companies. The current focus of litigation is the surge in patent challenges mounted by ANDA

applicants while the innovator drug manufacturer's patents on the approved drug or its use are still in place. These so-called 'Paragraph IV disputes' have become increasingly complex over the past 20 years and continue to grow.

Many Paragraph IV patent challenges are mounted against not only the basic patents on the active pharmaceutical agent and its original formulation, but also second-generation patents. The FDA has promulgated regulations governing the types of patents that should be listed in the Orange Book. Second generation pharmaceutical patents typically seek to claim 'listable' improvements upon the primary drug compound patent that include pharmaceutical formulations, such as sustained-release or combination formulations; new methods of use, ie new indications or patient populations; new dosing regimens and new methods of manufacture.<sup>13</sup>

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Innovators argue that second generation drug products provide improved effectiveness, safety, and ease of use for the patient and that the patents underlying the products provide valuable follow-on protection. ANDA applicants disagree. They argue that the second generation drug patents are overreaching attempts to extend the innovator's exclusivity and to maintain the high profits available for branded drug products before generics enter the marketplace, with little improvement or benefit to the public. Pharmaceutical companies seeking to protect their innovator drug products and to manage the life-cycle of their drug products, aware of these targeted litigation efforts, focus their attention on

8 The extension compensates the patent owner for a part of the time the patent was not protecting the market because the drug was not yet approved. It does so by moving a part of the ineffective patent term to the effective patent term, ie when the drug is on the market. A maximum of 5 years can be restored to the patent term. The total patent term, with an extension, cannot exceed 14 years from the product's approval date 35 USC §156.

9 The Orange Book is available at [www.fda.gov/cder/orange](http://www.fda.gov/cder/orange).

10 21 USC §§355(j)(2)(A)(vii)(IV), 355(j)(2)(B)(ii). ANDA applicants can file other certifications, if they agree to seek approval only after the applicable patent(s) expires (Paragraph III certification), or if the term of the patent has already expired (Paragraph II certification), or if no patent accompanies the listed drug (Paragraph I). The lion's share of litigation is thus associated with Paragraph IV certifications.

11 35 USC §§271(e)(2) and (e)(1), respectively.

12 21 USC §355(j)(5)(B)(iii).

13 While the FDA does not review patents presented for listing in the Orange Book, it does specify the types of patents that must be listed. For example, patents claiming the active drug substance, pharmaceutical formulations and compositions, and approved methods of using the drug constitute proper listings, whereas patents claiming metabolites, intermediates, or packaging features of the approved innovator drug are not proper for listing. 21 CFR §314.53(b). The FDA has made clear that it does not review patents submitted by NDA holders to determine whether these patents comply with its regulations. 68 Fed. Reg. 36676, 36678-79 (18 June 2003).

effective patent strategies that will withstand the challenges of the generic drug industry.

Recurring themes can be extracted from the non-infringement and invalidity certifications made by generic drug applicants in ANDA applications involving second generation patents. First, care must be exercised in listing patents in the Orange Book and innovator companies should take appropriate steps to coordinate the listing of second generation patents claiming methods of use with the appropriate FDA approval for those indications. The Federal Circuit has held that an ANDA filing is not an act of infringement of patents covering unapproved indications.<sup>14</sup> Moreover, a so-called 'Section VIII' patent certification specifically permits a generic drug maker to omit or 'carve out' from the proposed generic labelling certain patented indications when the branded label includes more than one approved use. This strategy avoids generic labelling that could induce others to infringe an innovator's patent.<sup>15</sup> Innovators should, therefore, avoid specific use codes descriptions for listed patents, to limit the possibility of labelling carve-outs by generic applicants.

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Another regular feature of infringement actions involving second generation patents is a dispute over the construction of the claim terms regarding the characteristics of the improved second generation formulation. Because a generic product is not yet on the market when suit is initiated, the primary source of evidence for infringement must come from the ANDA. The innovator plaintiff bears the burden of proving patent infringement by a preponderance of the evidence and the ease with which infringement is proved may depend largely on how closely the second generation patent claims that recite specific activities track the bioequivalency data set forth in the ANDA and relied on by the ANDA applicant to characterize its generic product.<sup>16</sup> Litigation challenges, therefore,

often turn on the adequacy of the disclosure for the rate and extent of absorption of the improved formulation in the innovator's patent, with ANDA applicants cross-claiming either invalidity based on overbroad ranges or else non-infringement based on incomparable data profiles with the claimed profiles.

In both these cases, the best defence is to attack. Innovator patentees should gather as much usage data relating to the improved formulation's bioavailability as possible, include both in vitro and in vivo drug delivery characteristics in the patent specification. An innovator can jump two hurdles together with a well-equipped patent that provides claim support for proving that the ANDA applicant's data fall within the parameters claimed in the innovator's patent. If the second generation patent claims recite the parameters relied on to show bioavailability by the ANDA applicant, the innovator may prove infringement based on the ANDA itself.<sup>17</sup> The likelihood of achieving a broad claim construction of a sustained release profile or other improved formulation will be best assured when broad claim terms are supported, but not limited, by a disclosure characterizing the improved formulation in terms of proven bioequivalence parameters.

In contrast, problems can arise in trying to prove infringement of patent claims that recite parameters that are not directly obtained from the ANDA. In *Alza Corp. v Mylan Labs., Inc.*,<sup>18</sup> for example, the patent claims required that a certain amount of the active ingredient be 'delivered' to the patient. The court construed the claim term 'deliver' to refer to the rate of *in vivo* release of the innovator drug Ditropan in the patient's gastrointestinal tract, which could not be measured directly. Patent owner Alza was thus forced to rely on the in vitro dissolution profile data of Mylan's generic formulation as indirect evidence of in vivo release to prove infringement. The Federal Circuit held the patent non-infringed, based on Alza's inability to demonstrate a correlation between the ANDA's in vitro dissolution and its own in vivo delivery, as required by the patent claims. Wherever possible, innovators should draft second generation patent claims that will be directly infringed by the bioavailability information in the ANDA. Patent claims that recite the

14 See, for example, *Warner-Lambert Co. v Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003) (holding Warner-Lambert could not assert infringement by alleging that generic applicant Apotex would induce infringement of a patent that covered the popular 'off-label' use of its drug); *Allergan, Inc. v Alcon Labs, Inc.*, 324 F.3d 1322 (Fed. Cir. 2003) (precluding Allergan from suing generic applicant Alcon for infringement based upon a 'non-infringing' ANDA that seeks approval for a use different from that claimed in a listed patent).

15 21 USC §355(j)(2)(A)(viii), 21 CFR §314.94(a)(8)(iv).

16 See above note 7.

17 See, for example, *Purdue Pharma. v Endo Pharms., Inc.*, 438 F.3d 1123 (Fed. Cir. 2006) (patent in suit recited in vivo blood plasma concentrations parameters for Oxycontin's sustained-release formulation that defendant generic company relied on in ANDA to demonstrate bioequivalence and was found to be infringed).

18 464 F.3d 1286 (Fed. Cir. 2006).

drug's pharmacokinetic ranges, in terms of in vitro dissolution profiles rather than in vivo release, will be more likely to prevail on claims of literal infringement.

Innovator patentees in possession of broadly supported second generation patent claims must also be vigilant not to surrender any of the claims' valuable scope during the prosecution of their patents. Generic applicants are quick to seize upon—and raise as infringement defences—instances when a patent holder has limited the construction of a claim term during prosecution in an effort to obtain allowance. Such limitations can arise either directly, by disavowing a claim's scope, or more often indirectly, by amending a claim so as to surrender a claim equivalent that differs from the claimed limitation only insubstantially.<sup>19</sup> An ANDA applicant's assertion of this so-called prosecution history estoppel as an affirmative defense to infringement can prove arduous to overcome in litigation, particularly if the equivalent was 'foreseeable' by the innovator at the time of the amendment. An example of the difficulties that a patent owner may face in proving infringement under the doctrine of equivalents is seen in decision of the Court of Appeals for the Federal Circuit in *Glaxo Wellcome, Inc. v Impax Labs., Inc.*<sup>20</sup>

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In *Glaxo*, the second generation patent in suit claimed a sustained release formulation containing an admixture of bupropion (the active ingredient) and the hydrogel hydropropylmethylcellulose (HPMC), an agent used to impart controlled release characteristics to the formulation. Glaxo marketed this patented sustained release formulation as Wellbutrin SR for the treatment of depression and as Zyban for smoking cessation.<sup>21</sup> When Impax sought to market a generic version of a bupropion formulation containing hydroxypropylcellulose (HPC) instead of HPMC, the Federal Circuit affirmed

summary judgment of non-infringement of Glaxo's patent based on prosecution history estoppel. The Federal Circuit held that Glaxo, having narrowed the claims that had been directed to generic hydrogels to overcome an enablement rejection by directing the claims to HPMC, was estopped from asserting that HPC was an infringing equivalent of HPMC. The Court deemed HPC a foreseeable equivalent when the claim amendment was made, even though HPC was not disclosed in Glaxo's specification and could not therefore have been claimed, except as part of a genus.<sup>22</sup>

*Abraxis Bioscience, Inc., v Mayne Pharma., Inc.*,<sup>23</sup> represents a lone case where an innovator successfully dodged the foreseeability limitation of the rebuttable presumption of surrender and, thus, to the doctrine of equivalents in a Paragraph IV litigation. When ANDA applicant Mayne filed a Paragraph IV certification to market a generic version of AstraZeneca's Diprivana formulation using the antimicrobial agent 'pentetate', AstraZeneca sued for patent infringement both literally and under the doctrine of equivalents of its second generation patent that claimed a formulation of a sedative drug with an 'edetate' as an antimicrobial agent. The Federal Circuit reversed the district court's broad claim construction of 'edetate' as encompassing structural analogues including pentetate, pointing to AstraZeneca's claim language and patent specification, which the Federal Circuit held limited to edetate to its derivatives. As a result of this construction the district court's finding of literal infringement, which depended on the broad claim construction, fell. The Federal Circuit upheld infringement by equivalents, however, based in part on the finding that the antimicrobial activity of the pentetate was unforeseeable during prosecution. Thus, AstraZeneca's claim amendment during prosecution to edetate was held not to have surrendered patentability.

In the future innovator, patent litigants will likely need to prove that they could not reasonably have drafted a claim that literally covered the equivalent during the prosecution of their patent, with the success of infringement by equivalent claims turning on the unforeseeability arguments mounted by the innovators.

19 Under the doctrine of equivalents, patent claims that are not literally infringed, because the disputed product or process does not include all of the limitations contained in the claim may nevertheless be infringed if the differences between the disputed product or process and the claim limitations that are not literally present in the disputed product or process are 'insubstantial': *Warner-Jenkinson Co. v Hilton Davis Chem. Co.*, 520 US 17, 38–40 (1997). See also *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722 (2002).

20 356 F.3d 1348 (Fed. Cir. 2004).

21 *id.* at 1350.

22 Under the Supreme Court's *Festo* decision, claim amendments raise a rebuttable presumption of surrender of subject matter falling between the original and amended claims. One basis for rebutting that presumption is to show that the equivalent was not foreseeable at the time of the amendment: *Festo*, 535 US at 738; see also, *Ranbaxy Pharms., Inc. v Apotex, Inc.*, 350 F.3d 1235, 1241 (Fed. Cir. 2003) (prosecution history estoppel precluded reliance on the doctrine of equivalents because a narrowing amendment made for reasons related to patentability did not overcome the presumption that it had surrendered coverage of acetic acid as a foreseeable equivalent to formic acid).

23 467 F.3d 1370 (Fed. Cir. 2006).

Another clearly emergent trend in Paragraph IV disputes involving second generation patents is the Federal Circuit's recent expansion of the standard for patent invalidity based on the anticipation by inherency doctrine. Generally, a patent is invalid if it is expressly anticipated by a single prior art reference that discloses each limitation of the claimed invention.<sup>24</sup> A patent can also be implicitly anticipated by a reference that does not expressly disclose the claimed invention if one or more of the limitations of the invention that are not expressly anticipated by the reference are necessarily or inherently present in the reference.<sup>25</sup> It is not enough that the prior art would possibly or even probably produce the undisclosed characteristic; that characteristic must be the 'natural result' flowing from the prior art.<sup>26</sup>

In the pharmaceutical context, the Federal Circuit has broadened the inherency doctrine to allow recognition of the prior art's inherent characteristic long after the publication date of the prior art. For example, a patent claiming an antihistamine loratadine (the active component in Clarinex) inherently anticipated later claims to a metabolite that formed in the bodies of patients treated with that drug, even though the metabolite's existence was not previously appreciated.<sup>27</sup> Notably, some courts have recognized a distinction between the unpatentability of claims directed to an inherent property of a known compound that constitutes a mere added benefit of the prior art compound and patentable claims directed to a newly discovered use of a known compound.<sup>28</sup>

The Federal Circuit further sharpened the inherent anticipation doctrine by holding that second generation patent claims directed to an improved shelf life formulation, comprising the drug sevoflurane and a Lewis acid inhibitor (eg water) in an amount effective to prevent degradation of the drug, were inherently anticipated by the first generation patent claiming a

water-saturated sevoflurane composition.<sup>29</sup> The Court based its ruling on the meaning of 'effective amount' of the Lewis acid inhibitor and deemed any amount of water sufficient to anticipate both the product and the process for making the degradation-resistant formulation. In so holding, the Federal Circuit not only reaffirmed that inherent anticipation neither requires any prior appreciation of the beneficial nature of the product (ie water in the formulation), nor requires recognition of the purpose of the process, the method claims being invalidated for merely recognizing a new property of the prior art process.<sup>30</sup> Indeed, the Federal Circuit has repeatedly avowed that '[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent'.<sup>31</sup>

Another area in which second generation patents are susceptible to validity attacks is an assertion that the patents claim inventions that are not distinct from the inventions claimed in the first generation patent. Such patents would be invalid under a doctrine referred to as obviousness-type double patenting: this prohibits a patent owner from obtaining a second patent containing claims directed to the same inventive concept with different appearances or differing scope which are patentably indistinct from inventions claimed in an earlier commonly owned patent.<sup>32</sup> For example, where the later patent claims the same invention more broadly than an earlier patent, the later patent may be invalid for double patenting.<sup>33</sup> In *Perricone v Medicis Pharm. Corp.*,<sup>34</sup> patent claims directed to methods for treating damaged or aged skin were held invalid for double patenting in view of earlier claims to methods for treating sunburned skin. The Court reasoned that sunburn was a species of skin damage that rendered the broader claim invalid.<sup>35</sup>

It remains critical for pharmaceutical innovators to understand the rapidly changing nuances of second

24 35 USC §102. *Lewmar Marine, Inc. v Bariant, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987).

25 *Atlas Powder Co. v Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

26 *Continental Can Co. v Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

27 See, *Schering Corp. v Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure). The *Schering* court noted, however, that patentable claims could have been directed to the metabolite in its pure, isolated form or to a method of treating a patient by administering the metabolite or a pharmaceutical composition containing the metabolite. *id.* at 1381.

28 *Glaxo Group Ltd. v Teva Pharms.*, US Dist. LEXIS 16750 (D. Del. 2004) (holding a new use of the drug Zofran to treat nausea and vomiting patentable over a patent disclosing the drug as useful to treat migraine pain).

29 *Abbott Labs. v Baxter Pharm. Prods.*, 471 F.3d 1363 (Fed. Cir. 2006).

30 *id.* at 1368.

31 *Bristol-Myers Squibb Co. v Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

32 See, for example, *Eli Lilly & Co. v Barr Labs.*, 251 F.3d 955, 968, 972 (Fed. Cir. 2001) (methods of blocking serotonin uptake in brain neurons with fluoxetine [Prozac] invalid as double patenting over methods of treating anxiety with fluoxetine); *McNeil-PPC, Inc. v L. Perrigo Co.*, 337 F.3d 1362 (Fed. Cir. 2003) (obvious combination formulation of anti-diarrheal drug loperamide with the anti-gas drug simethicone [Imodium Advanced] to treat both diarrhoea and flatulence).

33 See, for example, *In re Goodman*, 11 F.3d 1046, 1053 (Fed. Cir. 1993) and *In re Berg*, 140 F.3d 1428, 1437 (Fed. Cir. 1998) (both cases affirming that an earlier species claim anticipates and therefore is not patentably distinct from a later genus claim).

34 432 F.3d 1368 (Fed. Cir. 2005) (summary judgment of invalidity affirmed on remand, Case No. 3:99 cv-1820 (CFD), D. Conn., 20 March 2008).

35 The Court noted that the double patenting defect could have been cured if the patent owner were to file a terminal disclaimer, surrendering the term of the patent that extended beyond the expiration date of the earlier patent. *id.* at 1375. A terminal disclaimer may not always be available, however, to cure obviousness-type double patenting.

generation patent infringement law. Whether the Federal Circuit will continue to expand the bounds of inherent anticipation, continue to restrain the doctrine of equivalents, or perhaps rely on the foreseeability limitation in deciding future Paragraph IV disputes remains unknown. But what is certain is that the overall harshness of the recent string of Federal Circuit rulings places an equal premium on drafting enabling patent applications, with as many different types of original patent claims as possible, and on ensuring that claim amendments are few and judicious. Skilled drafting efforts can also help to both avoid invalidity claims based on first generation prior art and to facilitate infringement proofs based on bioavailability data in an ANDA. Skilled prosecution efforts can help to maintain broad patent scope and coverage over foreseeable equivalents used by ANDA applicants. Though a daunting task, a carefully drafted patent specification, with extensive experimental support and careful prosecution, are worth the effort in the high stakes world of second generation pharmaceutical patent litigation.

## Part II: Europe and the UK

While the domestic law of the individual EU member state in which enforcement is carried out governs the infringement of a European patent, the principles of patent infringement in individual European countries are generally aligned with each other, and with the USA. Activities including the making, using, selling, offering for sale, and importing of patented products or processes are generally held to be infringing.<sup>36</sup> In the pharmaceutical context, drug companies benefit from the period of patent protection to keep generic competition off the market and to maintain profitable pricing structures, to recoup the costs of drug development.

Similarly to the USA, EU member states require extensive pre-clinical and clinical testing to ensure the efficacy and safety of a drug prior to marketing authorization. Accordingly, the effective patent-protected lifetime of a drug is substantially less than the patent term and competition is fierce to manage the drug's life-cycle. In contrast to the patent extension provisions under Hatch-Waxman, however, the Supplementary

Protection Certificate ('SPC') system in Europe is a relatively bureaucratic process, and may not offer additional protection beyond the patent term granted for second generation patents on improved formulations or combination products.<sup>37</sup> Thus, EU countries that have experienced the emergence of a strong pharmaceutical presence, such as the UK, place supreme importance upon patentable pharmaceutical advancements while generic drug companies are increasingly aggressive in their attacks on secondary or second generation pharmaceutical patents. This section examines the vulnerability of these patents in infringement actions.

As one of the most influential jurisdictions, the UK tends to lead other EU countries in interpretation of the threshold for patentability of pharmaceutical improvements. Many recurring themes emerge from the case law on what sorts of second generation pharmaceutical patents, such as new formulations and delivery systems, will withstand generic challenges. We examine new formulations, combinations of existing drugs, and new uses of existing drugs in turn.

New formulations of existing drugs are patentable under UK law. The English courts often revoke incremental inventions, however, as invalid for lack of inventive step. The UK's obviousness test involves a four-step analysis: (1) identify the person skilled in the art and the common general knowledge of that person at the time of the invention; (2) identify/construe the inventive concept of the patent claim in question; (3) identify the differences between the prior art and the inventive concept of the claim; and (4) determine whether these differences constitute inventive steps or whether they would have been obvious to the person skilled in the art.<sup>38</sup> The first step comprises, essentially, claim construction, which in the UK looks to the features of the claims and avoids seeking a generalized inventive concept from the patent specification.<sup>39</sup>

In *Cairnstores Ltd v Aktiebolegat Hassle (No 2)*,<sup>40</sup> the Court of Appeal for England and Wales considered whether two UK patents directed to sustained-release formulations of the blockbuster drug Losec (omeprazole) were invalid for obviousness. The second generation patents claimed a three-tiered drug, consisting of

36 See generally, European Patent Convention 2000 (EPC 2000).

37 See, for example, *Massachusetts Institute of Technology (MIT)*, Case C-431/04, European Court of Justice, 4 May 2006 (SPC only available for a single ingredient or a combination of active ingredients, not for an active ingredient in combination with an inactive ingredient). But Cf *Re Council Regulation (EEC) No 1768/92 [2008] EWHC 1902 (Pat)* (31 July 2008) (holding that an SPC is available for a combination of two active ingredients when the combination is protected by the basic patent but will not extend the use of one active ingredient on its own), <http://www.bailii.org/ew/cases/EWHC/Patents/2008/1902.html>.

38 *Pozzoli Spa v BDMO SA & Anor* [2007] EWCA Civ 588 (22 June 2007) (restating and refining the well-known test of Oliver LJ in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 (EWCA)).

39 *Unilever v Chefaro* [1994] RPC 567. Under *Unilever* and its progeny, elements of an invention which are not elements of the claim are irrelevant to determining obviousness.

40 [2002] EWCA Civ 1504.

the active compound encapsulated by an intermediate layer followed by an outer enteric coating. The patent for the active compound had expired and enteric coatings were known in the art. The intermediate layer was claimed to be the inventive step, functioning as a physical and chemical buffer to the enteric coating to provide sustained delivery of the active compound.

Adopting the 'problem and solution' approach commonly used by the EPO, the trial court held that it would have been obvious to try to determine whether the active inner core would interact with the enteric coating in a predictable fashion when the intermediate layer breaks down in the intestines. The Court of Appeal affirmed invalidity, relying heavily on the assessment by Laddie J of the skilled worker's knowledge of how to prevent coatings from reacting with active components. Moreover, the Court accepted Laddie J's use of the 'obvious to try' standard, holding that it would be obvious to try to use multi-layered tablets to keep incompatible components away from each other.

The 'obvious to try' test in the UK has its origins in case law dating back almost a century.<sup>41</sup> In the context of the pharmaceutical arts, however, the standard has been re-invigorated over recent years. This test is often employed in the case of second generation patents directed to combinations of existing drugs, where the problem and solution approach alone often does not suffice (given that the problem is always to find a better formulation of a pharmaceutical).<sup>42</sup> Recent cases leave pharmaceutical lifecycle management strategies by innovator companies in a parlous state. For example in *Mayne Pharma v Teva*,<sup>43</sup> a patent claiming an improved formulation of an ethanolic solution of paclitaxel was held invalid for obviousness, on the ground that a chemist skilled in pharmaceutical development would have sought to balance the pH of the active ingredient with an acidifying agent.<sup>44</sup> Similarly, a second generation patent claiming an inhaler administering a combined preparation of salmeterol (a known beta-adrenergic agonist) and fluticasone propionate (a known steroid) was revoked on the ground that, since inhalers using

steroid mixtures were known, it would have been obvious to try to combine inhalers with the two known ingredients to treat respiratory disorders.<sup>45</sup>

Against this backdrop, future attempts to secure patent protection on combination formulations might appear bedevilled. However, a recent case has recast the 'obvious to try' test in a new manner that prevents it from being applied too liberally or in hindsight. In *Saint-Gobain v Fusion Provida*, Jacob LJ stated that '[t]he "obvious to try" test really only works where it is more-or-less self-evident that what is being tested ought to work'.<sup>46</sup> Although not a pharmaceutical case, the 'self-evident' element of *Saint-Gobain* was quickly adopted in *Schering-Plough v Norbrook*<sup>47</sup> where the trial court upheld a patent directed to a pharmaceutical combination formulation, comprising a long-acting antimicrobial with an anti-inflammatory drug for the treatment of a range of infectious diseases: it would not have been self-evident that the combination ought to work to achieve a long-lasting effect.<sup>48</sup> Subsequently, several other pharmaceutical patent cases have employed the *Saint-Gobain* approach to obviousness and have found for the patentee.<sup>49</sup>

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*In the UK, the pendulum may have begun to swing back in favour of the pharmaceutical patent holder in the obvious-to-try context of second generation patents*

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In the UK, the pendulum may have begun to swing back in favour of the pharmaceutical patent holder in the obvious-to-try context of second generation patents. The likelihood of upholding a second generation patent covering a combination product or other improved formulation is strongest when the formulation produces an unexpected benefit that could not have been reasonably predicted without actual testing. A patent attorney should also be mindful not to draft combination product claims too broadly, in terms of the genus of drugs to be combined, in view of the rationale articulated in *Schering-Plough v Norbrook*.<sup>50</sup>

41 See, *Sharpe & Dohme v Boots* [1928] 45 RPC 153 (the so-called Cripps question) and *Olin Mathieson v Biorex* [1970] RPC 157 (would a skilled worker 'directly be led as a matter of course to try' the claimed invention).

42 See, *Beecham's (Amoxycillin) Application* [1980] RPC 261.

43 [2005] EWHC 2141.

44 Paclitaxel, known to be poorly soluble in water, was regularly supplied in a mixture. The Court deemed it obvious to try to add acid to a methanolic solution of paclitaxel to balance the pH and achieve improved stability.

45 *Cipla v Glaxo* [2004] EWHC 477. See also *Teva Pharmaceuticals and Others v Instituto Gentili SpA and Merck & Co Inc* [2003] EWCA Civ 1545 (holding a patent for the use of a bisphosphonate called alendronate or

its salt as the active ingredient in a pharmaceutical compound obvious over prior art that would be 'read . . . as an invitation to try alendronate in a pharmaceutical preparation').

46 [2005] EWCA Civ 177 at para 35.

47 [2005] EWHC 2532.

48 The claims covering long-acting oxytetracycline and flunixin (Norbrook's commercial product) were held to be valid, but the more general claims covering other combinations of antimicrobials and anti-inflammatories were found invalid for insufficiency.

49 See, for example, *Generics v Lundbeck* [2007] EWHC 2532 and *Actavis v Merck* [2007] EWHC 1311, see below note 54.

50 See above, notes 47 and 48.

The patentability of new uses of old compounds is another sensitive issue in the EU pharmaceutical arena, both at the level of European oppositions and infringement proceedings. Under European patent law, a second pharmaceutical use of a known compound is patentable.<sup>51</sup> However, in practice, the EPO and UK courts often apply a strict novelty standard to those claims, somewhat akin to the view of US courts with regard to inherent anticipation. While EU case law is in flux, in general, it has proved difficult to obtain EPO patents on second pharmaceutical uses of known compounds on the basis of recognized properties to obtain a similar (in the USA, 'leaning towards an inherent') effect. UK courts have set a similarly high standard for validity of such second medical use claims, showing a clear reluctance to enforce them against generic drug manufacturers.

For example, an EPO Board of Appeal held that a patent claiming a new use (prevention of skin atrophy) of a compound lacked novelty over a prior use of the active ingredient (treating dermatoses), even though the mechanism of the effect was not previously appreciated and the result had not even been attributed to the compound in the composition.<sup>52</sup> Using similar logic, the Court of Appeal for England and Wales held invalid second generation patent claims, directed to a new dosing regimen for the chemotherapy drug Taxol, as lacking novelty in view of the prior art first generation patent claiming a therapeutic use of the drug.<sup>53</sup> The Court characterized the new therapeutic purpose for which the substance was used as not being 'distinctly different' from the first therapeutic purpose (also treatment of cancer). The dosing protocol was insufficient to provide novelty. More recently, two UK rulings, *Actavis v Merck* and *Teva v Merrell*, have revoked second generation patents following this same reasoning.<sup>54</sup>

These British holdings are, however, at odds with the EPO Board of Appeal decision on Genentech's second generation patent for a new treatment regime for insulin-like growth factor (IGF-1).<sup>55</sup> In *Genentech*,

the Board upheld claims directed to the use of a composition for the manufacture of a medicament for a specified new therapeutic application (treating a chronic disorder through intermittent periods of administration of a therapeutically effective amount of IGF-1), while acknowledging that 'the novelty of the application might lie only in the dose to be used or the manner of application'. It is uncertain how this decision will be reconciled with the developing British case law.<sup>56</sup> Given this conflict pharmaceutical innovators in the EU should refocus their patent strategies where possible to avoid over-reliance on secondary use patents until further certainty is achieved in this area.

### Part III: Japan

Many elements of the Japanese patent system are similar to those of the USA and Europe. Together, those three jurisdictions are viewed as the world's leading patent systems. Japanese patent law seeks to reward innovation and effort, by providing that any person who has made an invention which is *industrially applicable* may obtain a patent, with a few statutory exceptions.<sup>57</sup> While the industrial applicability requirement serves to enforce the utility necessary for allowable subject matter, subject matter must be a 'novel and true invention' if it is to be patentable, defined in the Japanese Patent Law section 2(1) as 'a highly advanced creation of technical ideas utilizing a law of nature'.

In the pharmaceutical context, compositions and uses of pharmaceutical compositions are both patentable in Japan, as long as the claims are directed to the product itself, ie the pharmaceutical composition, or the traditional Swiss-type use claim, which is considered to be a category of process claims. Methods for the treatment of the human body and diagnostic methods practised on the human body are considered industrially inapplicable inventions.<sup>58</sup>

51 *EISAI/Second Medical Indication* G 5/83 [1985], OJ EPO 64. In *Eisai*, the Enlarged Board of Appeal of the EPO held that a European patent may be granted with claims 'directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application'. Now Article 54(5) of EPC 2000 expressly permits second-use claims in the form of 'compound X for treatment of disease Y'.

52 *Prevention of skin atrophy/Ortho Pharmaceutical* T 254/93 [1998] OJ EPC 285.

53 *Bristol-Myers Squibb v Baker Norton* [2001] RPC 1.

54 In *Actavis v Merck* [2007] EWHC 1311, Actavis successfully prevailed against Merck's European patent directed to the use of a low dose of Finasteride for the treatment of androgenic alopecia, for lack of novelty. In *Teva v Merrell* [2007] EWHC 2276, Teva successfully demonstrated that Merrell's patent for the improved use of Terfenadine and Aventis' and Sepracor's patents on the improved use of the acid metabolite of Terfenadine lacked novelty and inventive step.

55 *Method of Administration of IGF-1/Genentech Inc.*, T 1020/03 [2004].

56 Warren J noted this disparity between UK and EPO jurisprudence in *Teva v Merrell*, above note 54, paras 32–33 ('I do not consider that it is open to me to depart from the decision in *Bristol-Myers* [see note 53] . . . It is for that Court to consider whether its earlier decision should be departed from in the light of developing case-law in the EPO').

57 Japanese Patent Law section 29(1).

58 Inventions liable to contravene public order, morality, or public health are statutorily exempted from patentability under Japanese Patent Law section 32. Thus, while use claims are generally acceptable in Japan, claims to using compound X for the treatment of disease Y are considered close enough to method of treatment claims that, if practised on a human, may be rejected. H-R Jaenichen *et al.*, *From Clones to Claims* (Carl Heymanns Verlag GmbH, 4th edn, 2006), paras 22.12–22.12.4.

Thus, in order to obtain a second generation patent in Japan, claims must be directed towards the pharmaceutical composition itself, with qualifying language to include the necessary improvement, such as, *inter alia*, a new patient population for treatment, a new delivery system, a combination of two effective ingredients, or a combination treatment involving a new dosing regime.

Patent infringement is traditionally tried separately from patent validity. However, following Japanese Supreme Court guidance, Japanese courts are increasingly willing to entertain invalidity defences (cast as the 'offence of abuse due to evident invalidity') in patent infringement actions.<sup>59</sup> As such, a Japanese court may construe claims narrowly or even refuse to enforce the patent if the court criticizes the patent's validity.<sup>60</sup> In the drug industry, refusal to enforce a patent can cause devastating consequences for an innovator pharmaceutical company that benefited from the patent to keep generic competition off the market. Likewise, successful dismissal of an infringement action can greatly skew a competitive market in favour of generic drug manufacturers.

Japan, like most other sophisticated markets, requires extensive testing of a pharmaceutical product before granting marketing authorization. An extension on a pharmaceutical patent term is available for up to 5 years if the regulatory delay, ie the time during which the patented invention could not be 'worked' pending government approval, exceeds 2 years.<sup>61</sup> However, since such extensions are typically not permitted for second generation products (eg new dosage forms),<sup>62</sup> innovator pharmaceutical companies must employ a variety of strategies to increase market exclusivity for those products. Patent infringement actions in Japan employ both business and legal strategies where, in many cases, the outcomes have a critical impact on commercial activities for both innovator and generic pharmaceutical manufacturers.

Conventionally, the strategy of Japanese companies has been to obtain numerous patents, to protect the patent owners' products rather than to take action against competitors.<sup>63</sup> Likewise, Japanese courts have tended to construe patent claims relating to technologies in patent-dense fields narrowly and applying a strict literal interpretation to the claims. As a policy matter in Japan, the trade-off between allowing narrower claims that offered weaker protection to patentees, but created wider freedom to operate for subsequent innovators was deemed necessary to stimulate investment in the Japanese economy. Although the doctrine of equivalents exists in Japan, it comprises a difficult five-part test and determinations of infringement by equivalents are rare.<sup>64</sup>

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Generic drug makers are currently aggressively expanding their Japanese businesses, forcing innovator companies to pursue more aggressive and comprehensive second generation patent litigation strategies against impending generic competition. One example of this effect is the enforcement of Astellas Pharma's second generation patent directed to a crystalline form of cefdinir, an oral cephalosporin antibiotic, marketed as Cefzon for treatment of respiratory infections, against generic manufacturer Taiyo Yuhukin. Astellas' first generation patent on the cefdinir compound had expired and Taiyo had begun marketing a generic version of the oral cefdinir capsule. Astellas won the infringement action in the Tokyo District Court and was granted a permanent injunction.<sup>65</sup>

The trial court dismissed Taiyo's invalidity arguments on the grounds of lack of novelty and

59 See, *Texas Instruments v Fujitsu Ltd.*, Judgment of Supreme Court of Japan, Case No. Heisei 10(O) 364 (11 April 2000) (holding that a court has the ability to decide that the patent in suit is invalid, and deny the infringement suit on the theory of abuse of right, if it is well-nigh certain that the patent in suit would be invalidated by a decision following a trial proceeding).

60 Formal invalidation or nullity proceedings (appeal or trial) are before the Japanese Patent Office (JPO). However, a provision of Article 104-3 of the amended Japanese Patent Law of 2004 sets forth that the enforcement by courts of a patent that should be invalidated by the JPO should be restricted.

61 Japanese Patent Law section 67(2).

62 When approvals are granted to pharmaceuticals with the same active ingredient (product) and efficacy/effect (use) and differing only in manufacturing processes, dosage forms, etc., patent term extension shall be granted on basis of the earliest approval only. Japanese Patent Office,

Patent Term Extension Guidelines, p. 6, available at [http://www.jpo.go.jp/tetuzuki\\_e/t\\_tokkyo\\_e/Guidelines/PartVI.pdf](http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/Guidelines/PartVI.pdf).

63 In the pharmaceutical industry, Japanese patents have traditionally been enforced through licensing agreements rather than through the court system. See Reiko Aoki *et al.*, 'Patent Policy and Public Health in Developing Countries: Lessons from Japan', *Bulletin of the World Health Organization*, 84(5), 412–413 (2008), noting that major US firms claim the Japanese patent system often forces them to enter into cross-licensing contracts with infringing Japanese firms, rather than to litigate.

64 The landmark case that established the doctrine of equivalents in Japan was *Tsubakimoto Seiko Co., Ltd. v THK K.K.*, Case No. 1994 (O) 1083 (Japanese Supreme Court 1998). For a discussion, see M Takabe, 'Intellectual Property Litigation: Future Issues' (2), 22 *AIPPI Journal [Japan]* [No. 2] 93, 96 (March 2008).

65 *Astellas Pharma, Inc., v Taiyo Yuhukin Co. Ltd.*, Heisei 17 (wa) 19162, (Tokyo District Court 2007).

obviousness, reasoning that the crystal form of the compound was patentable because its existence, structure, and properties could not be predicted. Moreover, the court ruled that one crystalline form of a compound does not anticipate another as long as (a) a crystal with the same structure as the patented crystal is not disclosed in the prior art, regardless of the description of physical properties in the art and (b) a crystal producible by a prior art method is not structurally identical to the patented crystal. This decision was affirmed on appeal by the Intellectual Property High Court of Japan (IPHCJ).<sup>66</sup> In December 2007, the Japanese Supreme Court dismissed Taiyo's appeal, in its landmark ruling that a second generation patent on a crystal form of an existing compound can extend the effective patent life of a valuable pharmaceutical product.<sup>67</sup>

Under Japanese patent law, all patent claims are classified into product claims or method claims. Method claims are further classified into 'production method claims' or 'non-production method claims'.<sup>68</sup> Production method claims often accompany basic compound claims in first generation patents. Non-production claims can include, inter alia, a measuring method, a method of using a product, and a method of treating or detecting a product. These types of claims are somewhat akin to screening or diagnostic claims in the USA. Innovator pharmaceutical manufacturers should be mindful that they may be liable for infringement of such non-production methods in their production and marketing of second generation patents. These claims do not carry the breadth of product-by-process claims, however, because they are often only used temporarily during manufacturing.

For example, in *Nippon Zoki Pharmaceutical v Fujimoto Diagnostics*,<sup>69</sup> an innovator pharmaceutical product was found to infringe a patented measurement method because the method was used in the manufacture of the second generation pharmaceutical product. The Supreme Court, reversing the Osaka High Court decision, held that a simple measurement method claim did not cover the 'measured products', because the invention was directed to a method, not a process

resulting in a product. Moreover, the method was no longer being used in manufacturing of the second generation product. It was, by US standards, a research tool patent.<sup>70</sup> Although the infringement of research tool patents does not typically arise in innovator-generic litigation battles, the related issue of the experimental use of the innovator drug patent for the purposes of generic drug development does. Japanese courts have broadly exempted from infringement research conducted in advance of patent expiration to develop generic versions of patented (first or second generation) drug products to market and sell once the innovator's patent(s) expired.<sup>71</sup>

These holdings provide another thorn in the pharmaceutical innovator's side with regard to the enforcement of second generation pharmaceutical patents. Indeed, enforcement of second generation patents in Japan is often hampered for reasons beyond the strength of the patent itself. Among these reasons are a broad research exemption and a general lack of discovery in Japanese courts. Accordingly, Japan remains a far less litigious market than the USA. Nevertheless, innovator pharmaceutical companies seeking to manage the life-cycle of their commercial drug products must remain vigilant in their attempts to enforce second generation patents around the world, including in Japan.

## Smoke and incantations

[P]atent lawyers are asked to defend—with smoke and incantations when necessary—business-driven decisions having nothing to do with inventing or discovering anything. Consistent with schemes to prolong the legally-protected period of exclusivity, companies hire highly talented attorneys to perform acts of legal legerdemain in order to make modest developments look and feel like inventions, when in reality the purported discovery is nothing more than a creation of an advertising and marketing department.<sup>72</sup>

This paper has assessed the vulnerabilities of second generation pharmaceutical patents in the USA, UK, and Japan, in terms of both validity and the obstacles to

66 *Taiyo Yakuhin Co. Ltd. v Astellas Pharma. Inc.*, Heisei 19 (ne) 10034 (IPHCJ 2007).

67 For a discussion see, JA Tessensohn and S Yamamoto, 'IP High Court Enforces Crystal Form Patent', *I.P. Japan*, 18 Spring/Summer 2008, pp. 15–12.

68 S Yamamoto and JA Tessensohn, 'Enforcing Patent Exclusivity in the Global Market—The Japan Strategy', slide presentation from BIO Annual Meeting, 8 June 2004.

69 H 10 (ju) 604, (Japanese Supreme Court, 1999).

70 A research tool is any item or method useful in conducting experiments in a research setting. Research tools are regularly used in the

pharmaceutical industry. By contrast, research tool patents are often held by smaller biotechnology companies or research institutions that actively seek to out-license the technology to finance their early stage research.

71 *Ono Pharms. Co., Ltd. v Kyoto Pharm. Indus., Ltd.*, 30 IIC 448 (Japanese Supreme Court, 1999). See also Japanese Patent Law section 69(1) ('the effects of the patent right shall not extend to the working of the patent right for the purposes of experiment or research'). Similar provisions in UK and US law are not discussed in this paper.

72 *McNeil-PPC, Inc. v L. Perrigo Co.*, 207 F. Supp. 2d 356, 375 (E.D. Pa. 2002), aff'd in part, rev'd in part, *McNeil-PPC, Inc. v L. Perrigo Co.*, 337 F.3d 1362 (Fed. Cir. 2003).

proving infringement by generic products. Despite the difficulties inherent in obtaining and enforcing second generation patents, generic competition reduces the market share of innovator drug products (be they first or second generation products) so greatly that it remains of paramount importance for every innovator pharmaceutical company to implement a patent life-cycle management strategy that includes second generation patents.

Innovator drug companies and their counsel are highly sophisticated parties, readily capable of assessing not only the merits of their claimed inventions but also the expected profits as compared to the costs that would be incurred in the event that their patents were held invalid. Not only is the patent law for evaluating the appropriate tactics unsettled, but strategies that seek to extend market share or to delay the introduction of generic drugs are also susceptible to challenges under the antitrust laws. Thus, if a court finds that a second generation patent amounts to a scheme for extending the life of a drug about to lose its basic patent protection, a generic drug manufacturer could challenge the innovator's patenting scheme as being anticompetitive (in Europe and elsewhere) or a violation of the antitrust laws (in the USA). If the facts suggest and/or a court finds that an innovator patent holder intentionally subverted the objectives of the patent laws for the sake of profits, losing patent protection could be the least of the innovator pharmaceutical company's worries.<sup>73</sup>

Nevertheless, given the high stakes involved, we can expect litigation between innovator and generic drug manufacturers to continue to increase, particularly litigation involving second generation patents. Innovator pharmaceutical companies will continue to seek global patent protection for improvements they make to their drug products and for new indications using those products. They will continue to take steps to prepare and prosecute new patent applications worldwide so as to avoid the infringement and validity vulnerabilities of second generation patents. In contrast, generic drug manufacturers will find fresh ways to challenge those patents in order to achieve rapid entry into the marketplace. The case law in this field is in flux. New challenges appear almost weekly, both for the innovator pharmaceutical companies and their generic competitors, making it an exciting and challenging field in which to practise.

From a jurisprudential perspective, it has been said that '[i]t would shock one's sense of justice if an

inventor could receive a patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted'.<sup>74</sup> While not untrue, this bromide does not encapsulate the real considerations involved in patenting second generation pharmaceutical patents, nor does it appreciate the breadth and importance of possible patentable improvements to a basic drug product.

Conceptually, while second generation patents may not always provide the same degree of public benefit as a primary patent on a novel compound to treat a new disease, it is nevertheless unfair to castigate all second generation patented inventions as mere attempts to extend the high revenue of a profitable drug product. Second generation pharmaceutical products often constitute significant improvements over first generation products. They can improve the performance and attractiveness of drugs. They can be useful to identify new patient populations for treatment, improve the drug's safety or ease of administration, and provide fewer side effects and a better quality of life. It is not an overstatement to say that second generation pharmaceutical products can save the lives of patients who may not have been saved by a first generation product.

The dilemma regarding second generation patents can be summed up in the words of the Federal Circuit, when overturning an award of attorneys fees against an innovator manufacturer seeking to enforce a second generation patent that was deemed invalid: 'While it may be considered more socially desirable for companies to seek truly novel inventions for maladies not yet treatable, the patent laws set the standards of novelty, non-obviousness, and utility as the requirements for patentability, without making value judgments concerning the motives for making and attempting to patent new inventions of lesser medical value'.<sup>75</sup> The patent laws embrace a tension between the public interest and the capitalistic ideals of investment and profit. Ultimately, it is the patent laws that must guide our judgments about the enforcement of second generation pharmaceutical patents in the battle over global drug markets.

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73 For example, inequitable conduct charges are becoming near routine in ANDA litigations. See, for example, *McNeil-PPC, Inc. v L. Perrigo Co.*, 207 F. Supp. 2d at 375. ('Advancing a client's economic interests is not a license to forget one's ethical responsibilities').

74 *Geneva Pharms., Inc. v GlaxoSmithKline PLC*, 349 F.3d 1373, 1386 (Fed. Cir. 2003) (citation omitted).

75 *McNeil-PPC, Inc. v L. Perrigo Co.*, 337 F.3d 1362, 1373 (Fed. Cir. 2003).