

Biosimilars patent litigation in Canada and Japan: a comparative strategic overview and EU and US update

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Biosimilars are highly similar versions of reference biological products, some with the potential to be deemed 'interchangeable' by medicines regulatory bodies, such as the US Food and Drug Administration. Biosimilar patent litigation continues to evolve as biosimilars enter new global markets. This manuscript is the second part of a manuscript that took a look at patent litigation strategies in a more developed biosimilars market, the European Union (EU), and compared them to a developing biosimilars market, the US, where the litigation strategies are still unfolding. This second part includes patent litigation strategies in two other developing biosimilars markets, Canada and Japan, as well as provides product and litigation updates in the EU and the US.

Keywords: 351(k), interchangeable biosimilar, Federal Circuit, Japan Pharmaceuticals and Medical Devices Agency (PMDA), patent litigation linkage, subsequent entry biologic (SEB)

Introduction

Canada and Japan are two additional regions that developed legal and regulatory frameworks for approval of highly similar versions of previously approved reference biological products (RBPs), called 'biosimilars' or 'follow-on biologics'. Canada's medicines regulatory counterpart, Health Canada, began regulating biosimilars as 'subsequent entry biologics' (SEBs) following a guidance issued in March 2010, utilizing a hybrid approach to how it regulates its generic drug products, known as 'subsequent entry drugs' (SEDs) [1]. Like the European Union (EU), Canada's first SEB was Omnitrope® (somatropin), which was approved in April 2009 [2], prior to the SEB guidance. But Canada has only one other approved SEB contained in two separate SEB applications, infliximab (RBP: Janssen's Remicade)®, both originally submitted by Celltrion [3]. Canada's regulatory approach to biosimilars is most closely aligned with the EU but has taken a different approach with regard to extrapolation for infliximab than the EU and other countries where it is approved. Canada's biosimilar patent litigation provisions are similar to how Canada addresses its SEDs, which is also undergoing some possible internal revision to bring its pharmaceutical patent litigation linkage to be more closely aligned to other country's systems, such as the US. Japan's system for follow-on biologics, implemented by Japan's medicines regulatory counterpart, Pharmaceuticals and Medical Devices Agency (PMDA), is similar to Canada in that it is a hybrid of some approaches similar to the EU such as quality attributes based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, along with some Japanese litigation and product requirements that tend to favour RBPs, such as unique proprietary and non-proprietary names. Japan also licensed Omnitrope® (somatropin) early on to Sandoz in June 2009 following its FOB framework in March 2009 [4], and now has seven FOBs referencing five products including somatropin.

Biosimilar regulatory overview

While Health Canada may follow class-specific guidances developed by the European Medicines Agency (EMA) for biosimilar product reviews, Health Canada reviews SEB applications on a case-by-case determination in view of its Food and Drugs Act, regulation and guidance. Health Canada requires SEBs to demonstrate similarity comparing physiochemical properties, biological activity, immunochemical properties, specifications and stability. SEBs in theory rely on comparator data in addition to their own safety, quality and efficacy data, where a non-Canadian RBP may be used under certain conditions rather than a Canadian RBP. Once approved, an SEB monograph includes results of the comparison of the SEB to the RBP and indications for approved use, but Health Canada allows no claims for bioequivalence or clinical equivalence. While a sponsor may conduct clinical studies to support interchangeability, such decisions are a province issue. Health Canada does not support automatic substitution, because SEBs and RBPs may make manufacturing changes over time. Health Canada has a number of posted SEB guidances, the most recent one is 'Information and submission requirements for subsequent entry biologics (SEBs)', draft released in December 2015 [5].

Health Canada has distinguished itself by taking a different position on extrapolation of indications for biosimilar versions of infliximab compared to other regulatory authorities. Remicade® is indicated for adult patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (PsO), as well as in paediatric patients with CD and UC. While there are some differences between Celltrion's infliximab and Remicade when looking at certain sensitive *in vitro* assays, EMA and other regulatory authorities assigned more weight to other assays that they considered more clinically relevant and that demonstrated similarity. EMA also judged RA to be a sufficiently sensitive clinical model in which to detect potential differences. The US Food and Drug Administration (FDA) appears to be heading in that

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direction with the US submission for infliximab by Celltrion/Hospira as well, as supported in an Advisory Committee hearing that occurred on 9 February 2016 and was approved on 6 April 2016. Health Canada, on the other hand, allowed extrapolation for most indications but not CD or UC, due to those differences observed in some *in vitro* studies and potential differences in the mechanism of action of infliximab in the conditions, and the absence of clinical studies for those indications. Some debate continues in the medical community about whether the data in RA and AS would provide an adequate foundation for extrapolation to other indications.

Japan in contrast has in total nine biosimilars, referencing six products including one somatropin product, previously referenced [6]. Japan's regulatory scheme requires follow-on biologics to have highly similar quality (analytics using the active ingredient, preferably, or the drug product) that has no adverse impact on safety and efficacy to a previously licensed referenced product in Japan. Japan's quality attributes are derived from comparability/equivalence studies, which are based on ICH guidances and observed differences in the products from non-clinical and clinical studies, including comparability in terms of safety and efficacy, where pharmacodynamic/pharmacokinetic studies may substitute for efficacy studies. In these situations, safety including immunogenicity studies are considered, especially for the formation of antibodies. Japan has issued guidelines for quality, safety and efficacy, and marketing approval including post-approval pharmacovigilance, [7] non-proprietary and drug names, [8] questions and answers, and product-specific safety communications [9]. Most of these publications are only available in Japanese with English translations as noted or summaries in various PMDA presentations [10].

Biosimilar litigation strategies

Canada

Canada's SEB patent litigation pathway is similar to its generic drug patent litigation pathway. Canada's Minister of Health cannot grant a regulatory approval (called a 'notice of compliance' or 'NOC') to a generic/SEB filing (also known as a 'piggy-back' submission, which is based on a comparison to an innovator's product), until the applicant addresses all patents listed by the innovator on a list of patents called the Patent Register. In some cases, a generic/SEB applicant will allege that a listed patent(s) is invalid or will not be infringed when it markets its proposed product, and the innovator may challenge those allegations in the Federal Court. Such submissions will then trigger the Regulations, if the party that filed the patents to the Patent Register files a prohibition order to granting the NOC within 45 days, resulting in litigation. During the litigation, the Minister may not grant an NOC to the generic/SEB applicant. At the end of the proceeding or 24 months, the Federal Court can prohibit the Minister from granting an NOC to the generic/SEB until relevant patent expiry, if it decides the generic/SEB allegations are not justified. Otherwise, the generic/SEB can obtain an NOC, subject to addressing the other patents, which may or may not block approval.

Canada's provisions are brief but often lead to complex challenges in the context of this initial litigation phase. For instance, a generic/SEB applicant may challenge whether a patent is eligible for listing in the Patent Register or whether such listed patents need to be addressed by a particular generic/SEB

applicant based on timing. In addition, a generic/SEB applicant may assert that an innovator is liable to pay damages to the generic/SEB applicant following an unsuccessful proceeding under the Regulations. Some recent and upcoming examples of NOC challenges for SEBs to watch include *Amgen Canada et al. vs Apotex Inc* (RBP Neupogen® (filgrastim)) (T-2072-12) (NOC hearing date 26 October 2015, dismissed 10 November 2015 and appealed), *Sanofi-Aventis Canada Inc vs Eli Lilly* (RBP Lantus® [insulin glargine solution]) (T-2247-14) (NOC hearing date 24 May 2016), *Amgen Canada vs Samsung Bioepis Co, Ltd* (RBP Enbrel® (etanercept) (T-1283-15), and *Janssen Inc. Celltrion Healthcare Co, Ltd and the Kennedy Trust* (RBP Remicade® (infliximab)) (T-1478-15).

Regardless of the NOC outcome, the innovator can bring a patent infringement action or the subsequent entry applicant can bring an action to impeach the patent or make a counterclaim for invalidity when sued for infringement under section 60 of the Patent Act. The threshold for standing is relatively broad ('any interested party'), but the would-be impeacher must pay security for legal costs into Court, i.e. an estimate of the patentee's recoverable legal costs if they win. Such infringement/impeachment actions may proceed in as little as two years or sooner. This second wave of infringement litigations leads to the Canadian generic drug/biosimilar system being called a 'double jeopardy'-type litigation system, i.e. there are two patent infringement litigation opportunities/risks.

At one point, it appeared that a patentee could not launch an infringement suit against a subsequent entry applicant without an NOC or product launch, because an application for an NOC subsequent entry approval was not an infringement nor were there sufficient grounds to maintain an infringement claim. Following *Apotex vs Lundbeck* (RLD: Ciprallex® [escitalopram]), 2010 FC 807 (T-1407-09), however, it now appears that a patentee may be able to maintain a counterclaim of infringement in the absence of an NOC or product launch, if the subsequent entry applicant attempts to impeach based on non-infringement (but unclear if only invalidity).

The sequence of *Apotex vs Lundbeck* is somewhat unique and worth considering. Apotex filed an NOC, which was prohibited, and Apotex appealed. Prior to the appeal, Apotex filed an impeachment action against the patent including an argument for non-infringement. In response, the patentee filed a counterclaim for infringement. On motion to strike, the patentee admitted that there was no evidence that Apotex was infringing to date, and the action was based on Apotex's desire to invalidate the patent and previous NOC application, which was not granted. The judge allowed the counterclaim to proceed, on the basis that while infringement might be somewhat speculative at that time, the interest of judicial economy suggested a strong benefit to have infringement of the future product considered at the same time as the impeachment.

This decision may be distinguished, however, because Apotex's future product was easily defined and known to the parties based on the prior NOC submissions and non-infringement argument. Therefore, impeachment may not be an option filed concurrently with the NOC, if the generic applicant's medicinal products are not finalized to a stage for a proper infringement analysis.

Based on some more recent cases, it appears that the decision in *Apotex vs Lundbeck* may lead to more patentee counterclaims in impeachment actions, which may increase their potential use, cost and complexity in SEB actions. For example, Hospira and Celltrion brought impeachments for Janssen's Remicade® in March 2013. Celltrion obtained two NOCs for infliximab in January 2014, one for Inflectra® and one for Remsima®. But then in June 2014, Hospira took a cross-license to Inflectra®, and Janssen filed for judicial review, asserting that a patent listed after Celltrion originally filed must now be addressed for Hospira's Inflectra®, because of the cross-license (but not for Celltrion's Inflectra® or Remsima®). Hospira's NOC was then revoked with a trial date for 12 September 2016. The related patent case is *Hospira Healthcare Corp vs The Kennedy Institute of Rheumatology* (RBP Remicade® [infliximab]) (T-396-13).

Aside from NOC and impeachment, SEBs applicants may also consider filing certain pre-grant and post-grant patent proceedings in Canada. In a pre-grant proceeding, a third party may challenge a filed patent application using only published prior art documents accompanied by an explanation of why the art is pertinent under section 34.1 of the Patent Act or Protest pursuant to section 10 of the Patent Rules. In these proceedings, a challenger submits prior art plus a submission that questions patentability on a variety of grounds. In a post-grant proceeding, the petitioner moves for re-examination under section 48.1 of the Patent Act based on prior published art. Few SEB or biological applicants take advantage of these proceedings, however, because a third party is not permitted to communicate directly with the Examiner or Re-examination Board and is not even informed of any actions taken as a result of these interventions.

Japan

Much like Europe's oppositions, Japanese biosimilar patent challengers prefer to utilize an invalidation procedure to patent litigation. Japan's intellectual property resolution mechanism is a two-track system with the Board of Appeals of the Japan Patent Office (JPO) hearing trials for invalidation (post-grant patent proceedings), and the District Court hearing patent infringement actions [11]. Unlike the US and other jurisdictions, Japan has no prelaunch patent litigation process prior to generic drug or follow-on biological product launch. In addition, the PMDA will not approve generic drug or follow-on biological products before the substance or second medical use patents expire. As a result, the Japanese legal system experiences less generic drug or follow-on biological products patent litigation. This is the intent of the Japanese legal system because Japan wants to ensure a steady supply of pharmaceutical products and is concerned that patent litigation may remove generic drug or follow-on biological products from the market [12].

So in Japan, invalidation proceedings are generally the forum of choice to challenge patents. Invalidation actions are relatively fast, averaging approximately nine and half months, administered by the JPO Boards of Appeals panel, which consists of experienced appeal examiners. In an invalidation proceeding, a patent challenger may bring enablement and other obviousness analyses for complex technologies, including biotechnology products, and all grounds of invalidation may be considered. To avoid the invalidation, a patentee may demand that its patent claims are restricted or corrected. While a trial for invalidation is running, a judge may

suspend or permit a district court patent infringement lawsuit to run concurrently. Anyone may bring an action for invalidation, but each party bears its own attorney fees.

As a second option, a patent challenger may also bring an infringement action in district court. All patent infringement hearings are heard before the Osaka or Tokyo District Court, which have exclusive jurisdiction over different geographic areas. Both of the district courts have designated intellectual property divisions, with technical advisors to brief judges on the complex technical matters in patent infringement cases. Patent infringement hearings are held at one- or two-month intervals until the deliberations are complete, not over consecutive days as in other countries. The parties to the proceedings submit briefs and evidence and expert opinions at each hearing, but parties rarely bring live examination of witnesses, and judges rarely grant motions for preliminary injunctions. If a party appeals an infringement action, its appeal primarily focuses on the briefs and includes little oral argument.

In a patent infringement action, the district courts may judge the invalidity of patents using a clear and convincing standard, where the JPO handles the invalidity portion and the district courts the 'abuse of patents' invalidity. In these proceedings, a patentee may demand necessary measures to prevent an act of infringement, including disposal of the alleged infringing products and removal of the facilities used for the alleged act of infringement. Because patent rights are a type of property right in Japan, infringement constitutes a tortious act, where damages are calculated under a special provision that includes the presumption of negligence and a reasonable amount of loss, and there is a special court fee calculation for damages. Only parties with standing may bring an action for patent infringement.

European Union update

Since the first part of this paper [13], one additional biosimilar product has been approved in Europe, the Samsung Bioepis version of Enbrel® (etanercept) called Benepali®, approved on 14 January 2016. According to Samsung Bioepis, Benepali® will be gradually rolled out across all 28 EU Member States as well as the European Economic Area (EEA) Member States of Norway, Iceland and Liechtenstein. In accordance with a commercialization agreement signed in 2013 between Samsung Bioepis and Biogen, Biogen will lead the commercialization and distribution of Benepali® in the EU and EEA Member States. There do not appear to be any ongoing patent oppositions or litigations associated with this product at this time.

United States update

In the US, the regulatory authority, FDA will keep the existence of a filed application confidential until the product is approved or the applicant discloses its application. When the first part of this paper [13] was submitted for publication, there were four publicly-disclosed filed biosimilar applications: Sandoz's Zarxio® (filgrastim) (RBP Amgen's Neupogen®), Celltrion/Hospira Remsima® (infliximab) (RBP Janssen's Remicade®), Apotex's pegfilgrastim (RBP Amgen's Neulasta®), and Apotex's Grastofil® (RBP Amgen's Neupogen®). In addition, Hospira had indicated that it had submitted an application for filing in December 2015, Retacrit® (epoetin alpha) (RBP Amgen's Epogen® and Janssen's Procrit®), which Hospira later confirmed at or around March 2016

that FDA filed the application. In October 2015, however, Hospira announced that FDA issued a complete response letter and that Pfizer, which completed its acquisition of Hospira in the interim, intended to submit a complete response to FDA in the first half of 2016. Pfizer said that it did not believe that additional clinical studies appeared to be indicated. Also in October 2015, Sandoz announced that FDA had accepted for review its version of Amgen's Enbrel® (etanercept). In November 2015, Amgen stated that FDA has accepted for filing its biosimilar version of Humira® (adalimumab). There do not appear to be current litigations surrounding the latest Sandoz and Amgen filings, but a patent information exchange is likely occurring given the more recent trend for applicants to share their 351(k) application and provide some manufacturing information.

Initial US litigations under the Biosimilars Patent Cooperation and Innovation Act (BPCI Act) largely have focused on procedural issues related to the 'patent dance'. Initial US biosimilar actions were premature declaratory judgments by Sandoz for its biosimilar version of Enbrel® (etanercept) and Celltrion/Hospira's version of Remicade® (infliximab). In both cases, the courts determined that the patent challenges were premature and did not have standing, because the biosimilar product applications at issue had not been filed with FDA yet. As a result, more recent would-be biosimilar applicants do not appear to have taken this early filing route.

An initial procedural 'patent dance' litigation that was filed after the biosimilar application was filed is *Amgen vs Sandoz*, which concerns the first FDA-approved biosimilar application, Sandoz's version of Amgen's Neupogen® (filgrastim), called Zarxio® (filgrastim-sndz, a 'placeholder' non-proprietary name, which FDA is still evaluating). Amgen initially filed its procedural challenge in a California District Court a lawsuit under California's Unfair Competition Law and for conversion for failure to follow the default patent information exchange mechanism that would lead to pre-market patent litigation. In the same court, Amgen also moved for a preliminary injunction to prevent Sandoz's market entry of Zarxio® pending a disposition on the merits. Here, Sandoz chose not to provide its biosimilar license application within 20 days of FDA's notice of filing or other elements of the patent dance, yet ultimately provided Amgen with its biosimilars license application, resulting in the present lawsuit and a separate patent infringement suit for one patent, which has been stayed pending resolution of the procedural patent exchange suit. Sandoz disagreed with the Unfair Competition Law charge, arguing that the provisions of the default patent exchange and pre-market litigation are optional.

The California Court denied Amgen's motion for a preliminary injunction and motion for a judgment on the pleadings. In conjunction with this action, Amgen filed a citizen petition with FDA to request that FDA not file any biosimilar application in its discretion, unless the applicant agreed to follow all procedures under the patent dance. FDA denied this petition on 25 March 2015, pending any contrary outcome in the litigation. Amgen then appealed the lower court's decision.

The Federal Circuit heard oral arguments on the pleadings on 3 June 2015. The main issues in the case were whether a biosim-

ilar applicant needs to engage in all steps of the patent dance to take advantage of the biosimilars approval pathway, or whether some or all of the steps are optional, and whether a biosimilar applicant can only provide 180-day notice of commercial launch after approval of the biosimilars license application or if notice of an intent to market following application approval is sufficient.

Sandoz prevailed in the Federal Circuit for the most part with a decision written by Judge Lourie dated 21 July 2015, but there were dissenting in-part opinions by Judges Newman and Chen. Lourie's opinion affirmed dismissal of Amgen's state law claims, including unfair competition and conversion. Sandoz's counterclaims to permit it to launch its product prior to providing 180-day notice after FDA approval were vacated and remanded to the lower court to enter judgment consistent with the Court's interpretation of the BPCI Act with an injunction pending appeal to Sandoz through 2 September 2015, corresponding to 180 days after its FDA product approval.

Lourie concluded that a 351(k) applicant can choose not to disclose its application as required ('shall' means 'may' in this context), leaving only remedies of the declaration of infringement, validity, or enforceability of any patent that claims the biological product or use of the biological product. Such infringement action further may include infringement of process patents, if the failure to disclose is coupled with an intent to obtain approval and market, use, or sell the biological product claimed in the patent or use of the biological product claimed in a patent before expiration of the patent. And both infringement actions would permit the RBP holder to access the 351(k) application through discovery, Lourie noted.

Lourie further concluded that a 351(k) applicant must (here 'shall' means 'shall') only give 180-day advance notice of commercial marketing after FDA has licensed the product. Lourie denied Amgen's unfair competition claims (a California law-based claim), because the infringement claims are the only remedy. Lourie denied the conversion claims (also based on California law), because Amgen failed to establish the elements in particular that Sandoz could not reference Amgen's BLA, because it failed to disclose its 351(k) application in a timely manner. Finally, Lourie denied Amgen's preliminary injunction, because it was moot in view of the previous issues not being resolved.

Newman concurred and dissented in part. Newman said that she agreed that 180-day notice is mandatory and that it may only start with the approval of the 351(k). Newman disagreed, however, that the notice of acceptance of a 351(k) application is voluntary, arguing that it is a prerequisite to take advantage of the 351(k) approval pathway ('shall' means 'shall' in her opinion).

Chen dissented in part. He agreed that the 351(k) applicant's failure to supply its application after filing was not a violation, because the RBP holder may still sue for infringement. Chen, however, disagreed that 180-day notice is mandatory or a 'stand alone provision', arguing that it was part of the voluntary patent exchange and fell when the 351(k) application was not shared as contemplated under the BPCI Act.

Biosimilars for Healthcare Professionals

Both Amgen and Sandoz appealed and requested an en banc review, i.e. rehearing before the entire Federal Circuit, not a three-judge panel. Amgen agreed with Newman that 351(k) and manufacturing information must have been provided and the patent dance followed as a prerequisite for FDA to review and approve a 351(k) application. Amgen's concurrent emergency injunction pending and its en banc review motions were denied, and Sandoz launched on 3 September 2015. Sandoz, meanwhile, requested a review of the 180-day notice requirement tied to 351(k) product approval. But both en banc appeals were denied, leaving open the question whether the issue would be appealed to the US Supreme Court. Amgen did not appeal, but Sandoz did on the last day of its extended time to file its petition for certiorari on 16 February 2016. The US Supreme Court can decide on its own whether to accept a case for review. With the unexpected death of Supreme Court Justice Antonin Scalia, if the Supreme Court decides to hear the case, there is the possibility for a split decision with the eight remaining justices. Scalia, in particular, had a strict interpretation of the legislation, which at times cast a swing vote for the justices. On 16 March 2016, US President Barack Obama nominated Judge Merrick Garland, Chief Judge for the US Court of Appeals for the District of Columbia Circuit, as Justice Scalia's replacement. Given the proximity to Presidential elections, however, many believe that the Senate will not hold confirmation hearings until after the election.

A second ongoing biosimilar case under the BPCI Act is a continuation of the unsuccessful premature BPCI Act case brought by Celltrion/Hospira on behalf of its infliximab product. Here, Janssen proactively sued Celltrion/Hospira based on several patents in *Janssen vs Celltrion and Hospira*. In this case, Celltrion/Hospira timely provided Janssen their 351(k) application, but Janssen argued that certain required provisions of the BPCI Act were not followed, because Janssen asked for certain manufacturing information in connection with the 351(k) that was not provided. Celltrion/Hospira said sufficient manufacturing information was in the 351(k) already. Following the *Amgen vs Sandoz* Federal Circuit decision, Janssen moved for a preliminary injunction against Celltrion/Hospira to launch their biosimilar product until at least 180 days after FDA approval. Celltrion/Hospira have argued that the 180-day notice is not mandatory, if the 351(k) application is provided in a timely manner. The parties have stipulated to dismissal for the initial patents that were asserted in the case, so the main unresolved issue remains the product launch date after product approval.

At the District Court status conference in *Janssen vs Celltrion*, which followed the FDA Advisory Committee vote regarding the proposed approval of Celltrion/Hospira's infliximab biosimilar on 9 February 2016, Celltrion's counsel said that while Celltrion expected FDA approval in about four to eight weeks, Celltrion would not launch until after 29 June 2016, which is the expiration date of the patent covering the Crohn's disease indication of infliximab. Janssen has brought a motion to stay the litigation pending its appeal of the United States Patent and Trademark Office's (USPTO's) Patent Trademark Appeal's Board decision invalidating the patent covering the infliximab product (an inter partes review (IPR) action, discussed *infra*). Also pending is Janssen's motion to amend the protective order to allow it to assert claims regarding an additional patent that was not in the original case. Janssen argued that Celltrion cannot launch until 2 October 2016, but in view of Celltrion's imminent launch and

the absence of an injunction, the judge has a scheduling conference set for 19 May 2016 to address these issues.

In third and fourth ongoing biosimilar application lawsuits, Amgen sued Apotex on its biosimilar version of Neulasta® (pegfilgrastim) and then its biosimilar version of Neupogen® (filgrastim). Amgen sued Apotex on 6 August 2015 for its pegfilgrastim product, following a 351(k) application exchange on 31 December 2014, with an initial hearing date of 11 July 2016, where the 180-day notice provision was in dispute as well as two patents. On 9 December 2015, Apotex lost its lower court challenge related to the 180-day notice provision, which it has appealed to the Federal Circuit, and has asserted counterclaims for patent misuse or sham patent litigation based on the two patents, which represented all of the unexpired patents in Amgen's patent list. For one of the patents, Apotex told Amgen that it would not launch its product before the expiration of one of the other patents, and the second patent concerns a method of folding a protein that Apotex alleges is not relevant to any specific protein or its product. The Federal Circuit scheduled oral argument for this case on 4 April 2016. A similar lawsuit is unfolding for Apotex's filgrastim product, following a 351(k) application exchange on 4 March 2015, also with two patents in suit, one of the same patents overlapping with its pegfilgrastim product. Both cases are in claim construction mode.

In addition to these types of legal proceedings, there are several options for biosimilar applicants to challenge patents that are more similar to what is commonly pursued in Europe and Japan – post-grant patent type reviews before the USPTO. An ex-parte re-examination is a type of post-grant review that may be brought at any time after patent grant. Anyone can bring an ex-parte re-examination challenge and such party may remain anonymous. In an ex-parte re-examination, a patent's validity is challenged by establishing a substantial and new question of patentability, based on patents and printed publications, as well as claim scope statements made in court or before the USPTO. Ex-parte re-examinations are reviewed by the USPTO's Central Reexamination Unit (CRU). After an ex-parte re-examination request is filed, a third party is generally precluded from further involvement, except it may file a response if the patent owner rebuts the request for review. A negative CRU decision may be appealed by the patent owner to the Patent Trial and Appeal Board (PTAB) or Federal Circuit. There is no legal estoppel, i.e. preclusion of bringing the same arguments in federal court, but a CRU decision may make it more difficult to invalidate the patent in federal court.

An initial type of post-grant review must be brought within nine months after patent issuance or a broadening reissue. A third party initiates the challenge with any legal challenge to validity for any claim under the standard that more likely than not the claim is not valid. The USPTO's PTAB hears the challenge and such actions are typically completed within one year.

Following the nine-month post-grant review time period, an IPR proceeding may be brought. This type of post-grant review is most likely and was brought by Celltrion for an infliximab patent reference above that may be relevant to its infliximab biosimilar. As another example, more recently, Amgen brought an IPR for two patents related to Humira. Amgen's IPR, however, was denied in January 2016. An IPR is also a third-party type review, but the

review is limited to novelty or obviousness and may only be based on patents or printed publications under a preponderance of evidence standard. Like the post-grant review, the PTAB decides the challenge, and the decision may be appealed to the Federal Circuit. IPRs are generally completed within one year but have a maximum duration of 18 months.

A final type of patent litigation action that may be brought in the US is a Section 337 action before the United States International Trade Commission (ITC). These types of actions require litigants to allege as unlawful certain unfair practices in import trade, including infringement of intellectual property rights, and require a domestic industry in the US. The remedies for a Section 337 action are injunctive relief, i.e. product exclusion or a cease and desist finding, which does not include the possibility of damages. Section 337 actions permit broad discovery, but the findings have no preclusive court effect. These hearings are heard by administrative law judges (ALJs), and the decisions may be appealed to the Federal Circuit and may involve active participation by the Office of Unfair Import Investigations. The ALJ completes review within 10 to 12 months. A Commission Opinion and Remedial Order will then issue within 14 to 16 months, and there is the possibility for review by the President within 16 to 18 months.

Unresolved legal issues regarding biosimilars patent litigation

There are many unresolved legal issues regarding biosimilars patent litigation in the four areas considered: Europe, US, Canada and Japan. As market uptake of biosimilars improves and FDA approves more biosimilars, will there be greater incentives for testing biosimilar patents in Europe before the US, especially if there is a unitary patent and a Unified Patent Court? Once FDA approves interchangeable biosimilars, how will this affect European patent challenges, especially for bridging products? For Europe to maintain its biosimilar lead, will revised avenues be provided to make patent challenges more attractive, perhaps in the Unified Patent Court?

In the US, the BPCI Act's patent challenge mechanism is still not clear, in particular concerning whether the 180-day advance notice of marketing will continue to be found to occur only after FDA approves the 351(k) application. Because of this uncertainty and other potential procedural uncertainties, there may be unforeseen risks for a 351(k) applicant to launch 'at risk', i.e. before all of the potential patents at issue have been litigated to permit market entry. While certain post-grant patent challenges and the ITC look like potential venues in addition to federal courts for patent challenges, it is unclear how often these venues will be used for biosimilar patent challenges or how successful they will be. Finally, there are many unresolved regulatory issues, including FDA's unresolved non-proprietary naming policy and interchangeability requirements, which may impact future biosimilar patent challenges.

In Japan, there appears to be a predisposition for innovator products rather than generic or biosimilar drug products. Will such predisposition continue to make biosimilar patent challenges in Japan less frequent? Over time, it is unclear how Japan will reconcile its policy goals to reduce cost and improve access to essential medications with the general aversion for use of biosimilars over innovator products.

Finally, for Canada, how will the rebooted impeachment process affect prelaunch patent litigations, i.e. will there be more counter-claims? Will there be pressure to add finality to the proceedings under patent linkage to be more like other legal systems, especially in view of the Canada–Europe Comprehensive Economic and Trade Agreement (CETA), and how will this affect biological products?

Index of abbreviations/acronyms

IPR (inter partes review) – a trial proceeding conducted by the Patent Trial and Appeal Board (PTAB) at the United States Patent and Trademark Office (USPTO) to review the patentability of one or more claims in a patent only on a ground that could be raised under 35 U.S.C. §§ 102 or 103, and only on the basis of prior art consisting of patents or printed publications. The PTAB is created by statute and includes statutory members and Administrative Patent Judges. The PTAB is charged with rendering decisions on appeals from adverse examiner decisions, post-issuance challenges to patents, and interferences.

Unitary Patent – a proposed new type of European patent that would be valid in participating Member States of the European Union with such unitary effect registered upon grant, replacing validation of the European patent in the individual countries concerned. The unitary effect means a single renewal fee, a single ownership, a single object of property, a single court (the Unified Patent Court), and uniform protection, meaning that revocation as well as infringement proceedings are to be decided for the unitary patent as a whole rather than for each country individually.

Unified Patent Court – a proposed common patent court for participation of all Member States of the European Union that would hear cases regarding infringement and revocation proceedings of European patents (including unitary patents) valid in the territories of the participating states, with a single court ruling being directly applicable throughout those territories. Requesting unitary patents upon the grant of certain European patents will be possible from the establishment of the UPC.

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References 1 to 13 can be found on page 88.

Biosimilars patent litigation in Canada and Japan: a comparative strategic overview and EU and US update References (please see the full manuscript on page 60)

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