Trends and Developments

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Patent Litigation Trends in the Life Sciences in the US

While there have been a number of trends in patent litigation in the life sciences recently, in this chapter the authors focus on two particularly pressing and notable trends. First, the authors address the growing clamour around the proper "listability" requirements for Orange Book patents and comment on likely behaviour of generic applicants going forward. Second, now that some time has passed, the authors discuss the ramifications of the Amgen v Sanofi Supreme Court case on the use of invalidity for lack of enablement under Section 112 as a defence in life sciences litigation.

Orange Book listability will likely remain a pressing topic in Hatch-Waxman litigation

While always an important issue, the determination of whether a patent meets the requirements for listing in the Orange Book has recently taken on increased significance. The debate about the correct standard for "listability" and whether specific patents have been correctly listed in the Orange Book continues to play out in multiple fora. In the context of Hatch-Waxman innovator-versus-generic patent litigation, high-profile attempts to oust (or "delist") a patent from the Orange Book have already begun. The authors expect that such attempts will continue, with generic companies becoming even more aggressive with the types of patents that they target for delisting.

The "Orange Book" is an FDA publication with the official title, "Approved Drug Products with Therapeutic Equivalence Evaluations" and is a central component to Hatch-Waxman's patent resolution mechanisms. The Orange Book contains a list of patents that claim an innovator drug or a method of using it. Generic applicants seeking to market a drug referencing the innovator drug are obligated to address each and every patent listed in the Orange Book for the innovator drug that the generic seeks to reference. When a generic applicant chooses to challenge a patent listed in the Orange Book, the generic applicant generally must certify that the generic product will not infringe the patent, or that the patent is invalid or unenforceable (ie, a "paragraph iv" certification). The generic applicant is obligated to send notice of its certification to the NDA holder and patent assignee as well as a detailed statement describing the basis for its position. Critically, if a patent infringement suit is brought, the FDA is barred from approving the generic application for 30 months (the 30-month stay). The FTC periodically raises the concern that improper listing of patents in the Orange Book could give rise to unjustified stays of generic approval with alleged anti-competitive effects.

Consequently, ensuring that patents are properly listed in the Orange Book is of tantamount importance. The general requirements for listing a patent in the Orange Book are specified in the Hatch-Waxman statute itself. The Act directs that applicants must submit patent information for listing a patent that: "(I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent" or "(II) claims a method of using such drug for which approval is sought or has been granted in the application" (21 USC Section 355(j)(2)(A)(iv)). In addition, the Act requires submitting patent information only for patents where "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug...". Within the broad category of "drug", the FDA has long-stated that drug substance (ingredient) patents and drug

product (formulation and composition) patents are properly listable, while methods of manufacture and process patents are not properly listable. Then, after prompting from the FTC in 2002, the FDA further determined that polymorph and product-by-process patents are properly listable, but patents claiming packaging, metabolites and intermediates are not.

While the FDA was able to describe several baskets of properly listable patents, it soon found that the line between "packaging" and some types of complex pharmaceutical products was harder to draw. For example, industry urged the FDA to clarify whether patents claiming device components of drug–device combination products like pre-filled syringes and metred dose inhalers were properly listable. Proponents of listability of device patents for these complex products contended that devices were not packaging – rather they were integral to the approved dosage form. Responding to these comments in 2003, the FDA declined to categorically exclude patents covering devices. Rather, pointing to the Orange Book appendix that lists approved dosage forms, such as metred aerosols and prefilled drug delivery systems, the FDA found that the key factor was whether the patent claims the finished dosage form.

But the FDA's 2003 comments were largely its last words on the issue. Seeking additional clarity, a number of innovators asked the FDA to provide advisory opinions about whether certain categories of device patents were listable. In particular, among other related issues, innovators asked the FDA to clarify whether it was necessary for a patent to specifically claim or mention the active ingredient in the drug product. The FDA has not responded, however, and has not otherwise provided guidance to industry on this issue.

While the Agency has remained silent, the issue of whether patents are properly listed in the Orange Book more recently has started falling in the lap of courts. In 2020, the issue of whether a patent claiming "a drive mechanism in a drug delivery device" was properly listed for Sanofi's Lanus (insulin glargine) SoloSTAR product was determined by the First Circuit in the context of an antitrust litigation (In re Lantus Direct Purchaser Antitrust Litig., 950 F.3d 1 (1st Cir 2020)). In the Lantus case, antitrust plaintiffs contended that the alleged improper listing of the drive mechanism patent was anticompetitive conduct. The district court dismissed the complaint, but the First Circuit reversed the dismissal, finding that the patent-at-issue did not meet the listing criteria. The First Circuit commented that the patent did not claim, let alone mention, Lantus SoloSTAR or insulin glargine. Consistent with the FDA's 2003 comments, the First Circuit distinguished between a component in a device (like a drive mechanism) and the finished product itself (for example, the injector pen).

Notwithstanding the FDA's silence, the Federal Trade Commission has again turned up the heat on innovators, starting with its September 2023 policy statement. In the FTC's policy statement, it announced that it would scrutinise improper Orange Book listings and warned that improper listing could give rise to civil and criminal liability. But critically, the FTC did not articulate the standards for proper listing in its policy statement. Soon thereafter, the FTC issued two sets of challenges (November 2023 and April 2024) identifying specific innovators, products and patents that the FTC alleged were improperly listed. Simultaneously with these challenges, the FTC also initiated the FDA's patent information dispute pathway for the patents. In response to the FTC's challenges, some innovators voluntarily delisted the challenged patents.

Just weeks after the FTC issued its policy statement, Teva sued Amneal in the District of New Jersey for patent infringement of six patents listed in the Orange Book for ProAir® HFA (albuterol sulfate) inhalation aerosol. The patents generally were directed to the dose counter component of an inhaler – all patents that were challenged by the FDA just a few weeks later as improperly listed. In response, Amneal availed itself of Hatch-Waxman's counterclaim delisting provisions to seek an order requiring Teva to delete the patent information on the ground that the patents do not claim the drug for which the application was approved (see 21 USC Section 355(j)(5)(c)(ii)(II)). Teva moved to dismiss Amneal's delisting counterclaims and Amneal cross-moved for judgment on the pleadings.

At the district court level, Judge Chesler denied Teva's motion to dismiss and granted Amneal's cross motion, finding that the Orange Book patents were not listable. Judge Chesler found that the case turned on whether the patent claimed the drug for which the applicant submitted the application, as required by the Hatch-Waxman statute. Judge Chesler found that the drug for which Teva submitted its application was albuterol sulfate inhalation aerosol. Thus, according to Judge Chesler, patents claiming a dose counter component of an inhaler did not claim the drug for which Teva submitted the application – rather, it only claimed a component.

On appeal, Teva warned of far-reaching consequences if the Federal Circuit allowed Judge Chesler's opinion to stand. For example, Teva contended that Judge Chesler's logic would result in the delisting of many patents that are commonly accepted as properly listable, including patents claiming chemical genera, novel inactive ingredients or dosage forms, or patents claiming one of multiple active ingredients. To the extent that the Federal Circuit does not reach the listability of these types of patents, we may see that generic applicants become increasingly aggressive in asserting delisting counterclaims. Thus, the authors expect to see generic applicants seek to delist not only the types of patents that the FTC has challenged recently (eg, device patents) but also for any patent that does not expressly recite the active ingredient, such as for chemical genera and formulation platform patents.

In December 2024, the Federal Circuit affirmed the district court order delisting the challenged Orange Book patents (Teva Branded Pharm. Prods. R&D v Amneal Pharms. of NY, LLC, 124 F.4th 898 (Fed Cir 2024)). A unanimous panel rejected Teva's principal arguments. The Federal Circuit rejected Teva's argument that the statutory term "claims" was effective coterminous with an infringement analysis as well as Teva's argument that the definition of "drug" in the Federal Food Drug and Cosmetic Act contemplated that components of a drug were individually considered "drugs" under the statute. As of the time of submission, Teva has petitioned the Federal Circuit for en banc review of the panel's determination.

Innovators should anticipate challenges to Orange Book listing and prepare in advance. Such preparation should include a critical evaluation of the basis for listing all patents in the Orange Book. For many patents, the justification for listing is likely relatively straightforward. Special care should be taken to justify patents that are listed relating to device components of drug–device combination products. In addition, innovators should confirm the basis of listability for any patent that does not expressly claim the active ingredient, even if that patent is a type that has been commonly accepted as listable, such

as chemical genus patents, or formulation platform patents. Innovators should also consider having a strategic plan ahead of time should a generic applicant challenge an Orange Book patent, either through a delisting counterclaim during litigation or otherwise through the FDA's dispute mechanism.

Wands factors remain as a key test for enablement post-Amgen

The specification of a patent is required to provide "a written description of the invention, and of the manner and process of making and using it... as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same..." (35 USC Section 112(a)). This requirement is commonly referred to as the enablement requirement. Although the Supreme Court does not often hear patent cases, it revisited the enablement requirement last year in Amgen v Sanofi in the context of patent claims that broadly covered all antibodies that functionally meet certain binding requirements (antibodies that (i) bind to specific amino acid residues on PCSK9, and (ii) block PCSK9 from binding to LDL receptors) (Amgen Inc. v Sanofi, 598 US 594, 143 S. Ct. 1243 (2023)). The Supreme Court unanimously affirmed invalidity of these broad functional antibody claims for failure to meet the enablement requirement for the full scope of the claim.

The Court in Amgen reiterated that "[i]f a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class", or simply, "[t]he more one claims, the more one must enable." The claims in dispute in Amgen potentially encompass a vast number (at least millions) of antibodies. The specification described 26 antibodies and provided a step-by-step "roadmap" for how to identify additional antibodies within the scope of the claim. The Court analogised disclosure of the "roadmap" to a combination lock with 100 tumblers, each of which can be set to 20 different positions, and require significant amounts of trial-and-error to discover the successful combinations. The Supreme Court considered this type of disclosure to be no more than "a hunting license" for "random trial-and-error discovery", which is not enablement.

The Supreme Court's holding in Amgen suggests that broad functional claims are more susceptible to invalidity challenges for lacking enablement. Since the Amgen decision, the Court of Appeals for the Federal Circuit has invalidated broad genus claims in four out of five decisions applying the enablement standard under Amgen. In these post-Amgen decisions, the Federal Circuit extended the analysis of Amgen beyond antibody technologies and reinforced use of the Wands factors for evaluating the enablement requirement.

The first decision from the Court of Appeals for the Federal Circuit that applied the enablement standard post-Amgen is In re Starett, which is a non-precedential decision arising from the Patent Trial and Appeal Board ("the Board") affirming rejections by an examiner of pending claims before the United States Patent and Trademark Office (USPTO) (In re Starett, 2023 US App LEXIS 14231 (Fed Cir 2023)). The claims at issue in Starett are related to methods and machines for maintaining augmented telepathic data that includes data structures representing categories of biological signals in a body such as "Nervous System" and "Sensory System". The specification disclosed a broad and abstract organisational structure used to accomplish the maintenance of augmented telepathic data, but

provides little guidance as to what type of devices are encompassed by the claims and how the devices would function. Citing to Amgen, the Federal Circuit concluded that "[h]ere, much is claimed and little is enabled" and affirmed the rejections of the claims as lacking enablement. Although this first post-Amgen decision from the Federal Circuit is non-precedential, it provides a first glimpse that the ramifications of the Supreme Court's holding in Amgen may extend beyond antibody technologies.

Shortly after Starett, the Court of Appeals for the Federal Circuit, in a precedential decision, extended the Supreme Court's analysis from Amgen beyond antibodies technologies to invalidate a method of treatment claim that functionally claimed clinical results (Medytox, Inc. v Galderma S.A., 71 F.4th 990 (Fed Cir 2023)). In Medytox, Inc. v Galderma S.A., the claims at issue are directed to a method for treating glabellar lines using an animal-protein-free botulinum toxin composition that "requires a responder rate at 16 weeks after the first treatment of 50% or greater." The specification provided three examples of responder rates above 50% at 16 weeks: 52%, 61% and 62%. During proceedings before the Board, the patent challenger provided expert testimony indicating that achieving the claimed 16-week responder rates is unpredictable, and that one skilled in the art would not have been able to achieve responder rates significantly higher than the exemplified 62% responder rate using the claimed animal-protein-free botulinum toxin formulations without undue experimentation (Galderma S.A. v Medy-Tox, Inc., 2021 Pat. App. LEXIS 4717 (PTAB 2021)). Relying on Amgen's explanation that "[t]he more one claims, the more one must enable", the Federal Circuit affirmed the Board's finding that "the arguments and evidence were insufficient to demonstrate enablement to a skilled artisan because said artisan "would not have been able to achieve" responder rates higher than the limited examples provided in the specification" (Medytox, Inc., 71 F.4th at 999).

It was not a long wait to see the impact of Amgen in a subsequent antibody decision. In Baxalta Inc. v Genentech, Inc., the Federal Circuit affirmed the district court's summary judgment of invalidity of claims reciting an isolated antibody that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa for lacking enablement (Baxalta Inc. v Genentech, Inc., 81 F.4th 1362 (Fed Cir 2023)). The specification in Baxalta describes eleven antibodies with the two claimed functions and a hybridoma-and-screening process for identifying additional antibodies that meet the claimed functions. In rejecting the hybridoma-and-screening process as enabling disclosure, the Federal Circuit noted that "Amgen makes clear that such an instruction, without more, is not enough to enable the broad functional genus claims at issue here." Here, the court was looking for additional guidance from the specification, such as common delineating features or explanation of why the disclosed antibodies worked, to identify which antibodies would perform the claimed functions, but did not find such guidance in the specification.

In view of the lack of any additional guidance in the specification, the court concluded that "[t]he facts of this case are materially indistinguishable from those in Amgen." The Federal Circuit stated that the trial and error testing necessitated by the specification "leaves the public no better equipped to make and use the claimed antibodies than the inventors were" when they set out to discover them. While the court in Baxalta relied on Amgen as the basis for its holding of invalidity, the Federal Circuit clarified that Amgen did

not disrupt prior enablement case law, including the longstanding Wands factors.

In another non-precedential opinion, In re Pen, the Federal Circuit provided a further glimpse at the potential expanded applicability of Amgen to broad claims beyond antibody technologies (In re Pen, 2024 US App LEXIS 14235 (Fed Cir 2024)). The claims at issue in Pen were directed to a chemical composition, a polycylic metallole heteroatom rich conductive long chain polymer, having a particular chemical structure containing n number of repeating units, each unit containing a number of R groups where "R is any substituent, and x is the number of R substituents." In rejecting the claims at issue, the USPTO examiner applied the Wands factors and discussed reasons why a skilled artisan would not be able to make and use the claimed invention without undue experimentation. This rejection was upheld by the Board and affirmed by the Federal Circuit. The Federal Circuit relied on Amgen to explain that "[i]n short, the more you claim, the more you must explain", and affirmed the Board's rejection of the pending claims for lack of enablement.

Most recently, the Federal Circuit affirmed the district court's determination of enablement for claims to a pharmaceutical composition comprising a combination of valsartan and sacubitril or sacubitrilat (Novartis Pharms. Corp. v Torrent Pharma Inc, 2025 US App. LEXIS 486 (Fed Cir 2015)). Some recent district court decisions also shed some light on distinctions from Amgen that support a finding of enablement. For example, in Regeneron Pharma v Mylan Pharma, the district court held that claims for an ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist was sufficiently enabled by the description provided in the patent specification (Regeneron Pharm., Inc. v Mylan Pharm. Inc., 714 F.Supp.3d 652 (N.D.W.Va. 2023)). The district court distinguished the facts of this case from Amgen because "[h]ere, in contrast, the claims are directed to formulations of a specific protein at a specific concentration – not "an entire kingdom" of proteins." The claims recite specific structures, and the specification provides examples and lists of excipients and amounts to use. The district court relied on expert testimony and applied the Wands factors to reach the conclusion that "the Defendants have failed to demonstrate by clear and convincing evidence that the asserted claims of the Product Patent are invalid for lack of enablement."

More recently, in Supernus Pharma v Torrent Pharma, the district court applied the Wands factors and held that claims directed to sustained release formulations of topiramate "which is released immediately and continuously upon administration from the formulation" and where the extended release component "exhibits a maximum plasma concentration of topiramate in vivo at 16 or more hours after a single initial dose" met the enablement requirement (Supernus Pharms., Inc. v Torrent Pharms. Ltd., 2024 US Dist LEXIS 49856 (DNJ 2024)). In upholding validity of the claims, the district court distinguished this case from Amgen in two meaningful ways: (i) the claims do not encompass an entire genus of release-controlled coatings regardless of physical characteristics or chemical properties; and (ii) expert testimony indicating that it would have been routine to adjust the coating precisely to achieve a desired release rate once a first in-vitro dissolution test has been conducted.

In view of the developing post-Amgen case law, patentees should anticipate invalidity challenges alleging lack of enablement and prepare litigation strategy in advance. Such preparation

should include a review of the claims asserted and the scope of species encompassed by the claims. In particular, consider whether the claims asserted recite structural elements in addition to functional limitations. The patentee should also conduct a thorough review of the specification to identify any guidance for identifying which species would fall within the scope of the claims and which species would not. As demonstrated in the district court cases discussed above, expert testimony can be probative in an enablement analysis. Therefore, patentees should also prepare ahead of time to present expert testimony and other evidence for each of the Wands factors in support of enablement.