molecular pharmaceutics

reviews

An Overview of Pharmaceutical Cocrystals as Intellectual Property†

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Received January 1, 2007; Revised Manuscript Received March 15, 2007; Accepted March 26, 2007

Abstract: This review article focuses on the interaction among certain scientific, legal, and regulatory aspects of pharmaceutical crystal forms. The article offers an analysis of pharmaceutical cocrystals as patentable inventions by drawing upon recent scientific developments in the field. Several potential commercial advantages of pharmaceutical cocrystals are highlighted, and a number of recent court decisions involving salient issues are summarized. The article provides an outlook on how the developing field of cocrystallization may impact the pharmaceutical intellectual property landscape.

Keywords: Pharmaceutical; cocrystal; solid form; polymorph; intellectual property; patent; legal; regulatory

I. Introduction

Patents and Pharmaceuticals. Identifying the optimum solid form of a pharmaceutical candidate is scientifically and clinically imperative.[1−4] Solid forms of drugs may exhibit undesirable physical properties, but experimental effort and creativity can reveal new forms with potentially advantageous characteristics.[5,6] Beyond polymorphs, hydrates, salts, and amorphous solids, a thorough solid form screen today may also include a search for cocrystals.[7,8] Pharmaceutical cocrystals have gained recent prominence in a flurry of research reports demonstrating that complexation of an active pharmaceutical ingredient (API) with another molecule can produce a solid form with different physical properties.[9−20] Compared to other classes of solid forms, cocrystals possess

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† Disclaimer: The views set forth herein are the personal views of the author and do not necessarily reflect those of Jones Day or its clients.

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10.1021/mp070001z CCC: $37.00
Published on Web 05/04/2007

particular scientific and regulatory advantages, and alongside these advantages are intellectual property issues which confer cocrystals with unique opportunities and challenges.

From software to fashion to pharmaceuticals, intellectual property (IP) protection is a critical element of industries in which the cost of product development substantially exceeds the cost of product manufacture. Pharmaceutical and biotechnology companies are particularly reliant on rigorous IP protection for safeguarding product revenues in an industry which combines extensive regulatory hurdles, high research and development costs, and inherent risks. The branch of intellectual property covering scientific and technological inventions is the patent system. Patents are a mechanism for promoting research for society's benefit: the right to exclude others from practicing a patented invention affords an economic incentive to the inventor, while the limited term of that exclusionary right ultimately delivers the invention into the public domain.

Although patentable subject matter in the U.S. was broadly interpreted by the Supreme Court to include "anything under the sun that is made by man",[21] a strict examination process scrutinizes each patent application in light of three necessary criteria for patent eligibility: novelty, utility, and non-obviousness.[22] Novelty requires that the subject matter of the claimed invention was not publicly disclosed, e.g., described in a single patent or publication anywhere in the world, prior to the date of the invention. Utility is a broadly defined concept, and generally includes any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof. Non-obviousness is a complex doctrine which is presently under review by the U.S. Supreme Court.[23] Essentially, a patent application will be rejected as "obvious" if the claimed invention would have been obvious to one of ordinary skill in the relevant art, e.g., upon combining information from multiple patents and/or scientific publications. Typical subject matter of pharmaceutical patents pertains to compositions of matter (e.g., a molecular entity, solid form, or formulation), methods of use (e.g., a particular medical indication), and processes of manufacture (e.g., a chemical synthetic route).[24]

The patent system is at the heart of an ongoing policy debate over balancing a productive, economically viable, research-based industry with an equitable system for maximizing citizens' access to effective pharmaceutical therapies. In the U.S., this policy balancing act is exemplified by the Drug Price Competition and Patent Term Restoration Act, known informally as the Hatch−Waxman Act after its congressional sponsors. Drafted in 1984 in response to a need for improved access to affordable pharmaceuticals, it contains provisions for both generic and innovator companies.[25] By facilitating the regulatory requirements of generic market entry, Hatch−Waxman has undoubtedly increased access to affordable generic drugs over the past two decades.[26]

In addition to fostering growth of the generic pharmaceutical industry, a further aim of the Hatch−Waxman Act was to maintain an incentive for research investment by providing innovator pharmaceutical companies with patent term extensions. A utility patent in the U.S. is valid for a 20-year period beginning on the initial filing date of the patent application,[27] but the exact time period for which an innovator pharmaceutical company will retain market exclusivity could be considerably less than 20 years. A patent application claiming the chemical structure of an API is typically filed well in advance of the API's regulatory approval and market launch (this tactic mitigates the risk that, while development

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(21) *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

(22) 35 U.S.C. §§ 101−103.

(23) *KSR International Co. v. Teleflex, Inc.*, 126 S. Ct. 2965, 2966 (2006).

(24) Grubb, P. W. *Patents for Chemicals, Pharmaceuticals and Biotechnology*; Oxford University Press: Oxford, 2004; pp 230−244.

(25) The Hatch−Waxman Act was amended as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

(26) See, e.g., *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, currently available at www.ftc.gov/os/2002/07/genericdrugstudy.pdf. Accessed Jan 1, 2007.

(27) In general terms, a "utility patent" pertains to function and use (35 U.S.C. § 101), while a "design patent" pertains to appearance (35 U.S.C. § 171). Design patents have a term of 14 years from the date of grant (35 U.S.C. § 173).

proceeds, a competitor could file an earlier patent application covering the same molecule). The 20-year patent-term clock thus starts long before the product reaches the market, and the time consumed by regulatory approval can be a major determinant of the total period of market exclusivity. For this reason, Hatch−Waxman specifically provides a limited patent-term extension to account for such "lost" regulatory time.

Beyond the Hatch−Waxman provisions and certain other opportunities for patent term adjustment, an effectively managed patent portfolio can also impact the market exclusivity of a pharmaceutical product. Such management can involve multiple patent filings covering different discoveries made during the development of a product, including its various solid form modifications. Patents on novel crystal forms of an API are valuable in this regard, and the investigation of different pharmaceutical solid forms, including cocrystals, is a growing area of research in which scientific advances can afford legal advantages.

II. Cocrystals as Inventions

Like the claimed subject matter of any patent application, a pharmaceutical cocrystal must be novel, useful, and nonobvious to be awarded a patent. A cocrystal is a distinct solid-state material with, in general, a unique and unpredictable structure and physical property profile.[1,7] A broad definition of cocrystals, "crystalline molecular complexes", encompasses hydrates and solvates: pharmaceutical crystal forms with a proven record of patentability.[28] Similarly, cocrystals in which the API is complexed with other types of countermolecules should also qualify as patentable inventions. Evaluating certain features that make cocrystals generally patentable helps reveal the importance of ongoing research into this emerging class of pharmaceutical crystal forms.

Novelty. Cocrystallization provides alternative solid-state modifications of APIs; in this regard, it serves a function identical with the more established technique of pharmaceutical salt formation. As new and distinct solid-state structures, cocrystals should satisfy the novelty requirement equally as well as salts.[29] A rough indication of the industry's interest in pharmaceutical salts is the extent to which they are mentioned in patents: a cursory search of the U.S. Patent and Trademark Office database reveals that over 24 000 issued U.S. patents contain the term "pharmaceutically acceptable salt" in one or more claims: indeed, the term has practically become patent boilerplate.[30] By contrast, cocrystals have apparently not yet achieved a comparable status: the same search for the term "pharmaceutically acceptable cocrystal" generates no hits.[31] The disparity does not imply a general difference in patentability; in fact, the relative paucity of patents involving cocrystals could suggest that the field is laden with opportunities for novel cocrystal inventions. Regardless, it seems clear that cocrystals which have not before been described should satisfy the novelty requirement for patentability.

While both salts and cocrystals may constitute novel inventions, a difference in the total number of possible salts and cocrystals for a given API amounts to a key theoretical advantage of cocrystallization over salt formation. The most important API solid form modifications are those that are acceptable for human ingestion. Marketplace precedence is one gauge of the apparent safety of salt-forming acids and bases; by this measure, a market survey in the mid-1990s revealed a limited number of acceptable counterions,[32] and the number and diversity of available pharmaceutical counterions has not markedly increased in the years since.[33]

In contrast to the relatively few suitable salt-forming counterions is an extensive list of potential cocrystal countermolecules. The U.S. Food and Drug Administration maintains a list commonly referred to as "Everything Added to Food in the United States", or EAFUS, which contains over 3000 substances, including ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as Generally Regarded as Safe (GRAS).[34] Administrative, chemical, and toxicological information is available for over 2000 entries, and many of the substances on this list appear to be suitable candidates for countermolecules in a screen for pharmaceutically acceptable cocrystals.

In theory, the total number of potential novel cocrystals far exceeds that of salts for a given API. In practice, however, each possible combination will not result in a crystalline salt or cocrystal. Without an understanding of which countermolecules will most likely form cocrystals with a given API, the experimental burden of a thorough cocrystal screen is daunting. To whittle down the list of potential countermolecules for a given API, studies that develop a predictive ability to identify successful countermolecules will be of great practical value. One promising approach for addressing this challenge involves analyzing the formation probabilities

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(34) This list is currently available on the FDA web site at http://vm.cfsan.fda.gov/~dms/eafus.html. Accessed Jan 1, 2007.

of prospective API:countermolecule supramolecular interactions using informatics tools such as the Cambridge Structural Database (CSD).[35,36]

Advanced synthetic approaches, such as high-throughput screening,[5] can also mitigate the experimental burden of cocrystal screening. Moreover, while traditional solution-based screening requires a great variety of solvent systems and crystallization conditions, thermal and mechanical methods may provide enhanced experimental efficiency. Kofler thermomicroscopy has been effective in this regard,[12,15] as has solvent-drop grinding.[37,38] Beyond efficiency, a secondary benefit of these approaches is structural diversity. Solid-state grinding, for instance, can provide novel cocrystals which are initially unattainable by solution-based screening methods.[39−42] Additional developments in screening methodology will further elevate the profile of cocrystals on the pharmaceutical and intellectual property landscapes.

Utility. As the subject of a U.S. patent application, a cocrystal of an API generally shares the patentable therapeutic utility of its parent API. In addition, recent research reports indicate that cocrystals can offer further opportunities for utility with respect to physical property improvements.

Solubility and dissolution rate profiles are suggestive of an API's bioavailability, which in turn can influence its overall therapeutic efficacy. Cocrystals with enhanced dissolution rates can therefore offer improved therapeutic utility. Cocrystals of the antifungal drug itraconazole with several pharmaceutically acceptable dicarboxylic acids exhibited dissolution rates greater that of crystalline itraconazole free base.[9] In fact, certain of these cocrystals exhibited dissolution rivaling that of amorphous itraconazole free base, prepared specifically for its improved dissolution profile. Another example involved perceived solubility enhancements in a series of three-component cocrystals involving the API salt fluoxetine hydrochloride (the active ingredient in the antidepressant Prozac) and several carboxylic acid countermolecules.[12] These studies may support the inference that highly soluble countermolecules tend to form cocrystals with improved kinetic solubility,[43] but confirmation of this phenomenon requires further study.

Other recent reports involving pharmaceutical development candidates have shed further light on the potential for cocrystals to offer enhanced solubility and bioavailability benefits. The measured solubility of an un-ionized succinic acid cocrystal of a cancer treatment candidate was greater than that of the free base but less than that of a partially ionized malonate salt and a fully ionized maleate salt of the corresponding API.[14] A glutaric acid cocrystal of a candidate for pain treatment provided a 3-fold improvement in the plasma levels of dogs as compared to the single-component API.[15] Further, an L-tartaric acid cocrystal of a phosphodiesterase-IV inhibitor provided over a 20-fold increase in the plasma levels of monkeys as compared to the API free base.[17] These reports exemplify a growing interest in cocrystallization as a means of obtaining improved therapeutic utility for pharmaceutical development candidates.

An API's physical stability is another key component of its regulatory approval, impacting formulation, manufacturing, and storage protocols. Research involving caffeine and the asthma drug theophylline illustrated that unstable APIs can form cocrystals with enhanced physical stability. While theophylline anhydrate converted to a crystalline monohydrate above 75% relative humidity (RH), a theophylline:oxalic acid cocrystal was physically stable at 98% RH, yet dissociated into its individual components at 100% RH and in water.[13] Several caffeine:acid cocrystals exhibited a wide range of physical stability; at one extreme, a caffeine:oxalic acid cocrystal was fully stable with regard to humidity and water.[38] The observed stability of this material is noteworthy, especially considering that both caffeine and oxalic acid, as single-component crystals, can individually convert to crystalline hydrates.

In addition to potential improvements in solubility, bioavailability, and physical stability, cocrystals—like any alternate crystal form of an API—may enhance a large number and variety of essential parameters, including hygroscopicity, chemical stability, compressability, and flowability, among others. A recent report mooted the possibility that cocrystals may reduce an API's susceptibility to polymorphism.[44] Using a limited definition of cocrystals,[45]

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the authors found that, among the approximately 1450 structures of hydrogen-bonded cocrystals in the CSD, only 11 entries were polymorphic; further, the identical supramolecular synthon was conserved within each pair of polymorphic cocrystals. Additional research will reveal whether this represents a genuine trend or a heretofore lack of investigation into polymorphism among cocrystals. Should this trend withstand further investigation, it would confer cocrystals with an additional commercial benefit. The unanticipated appearance of a new polymorph of an API can pose significant regulatory challenges.[46] Moreover, it seems possible that the risk of unanticipated polymorphism may never be fully eradicated: new polymorphs of single-component compounds have appeared many decades after their initial forms crystallized.[47−49]

Despite their apparent utility, cocrystals are not a panacea for physical property imperfections. As mentioned above, particular theophylline and caffeine cocrystals underwent dissociation, i.e., phase-separated into their individual constituents, upon storage at certain RH conditions.[13,38] Dissociation and precipitation also occurred upon dissolution of some of these cocrystals. Such dissociation behavior requires further study, but may present an important potential drawback to certain pharmaceutical cocrystals.

Another reasonable concern is whether cocrystals could possess a greater propensity for phase change during common pharmaceutical processing conditions. Grinding, particularly solvent-drop grinding, is an effective means of synthesizing cocrystals and interconverting among forms.[39] Grinding (e.g., in the form of milling) is also a common method of particle-size reduction in API manufacture. Consequently, cocrystals may carry heightened concern for phase change during pharmaceutical processing.[50]

Cocrystals may also possess susceptibility to "countermolecule displacement" with excipients during formulation. An early demonstration of solid-state grinding as a method of pharmaceutical cocrystal synthesis involved the drug sulfadimidine with various aromatic carboxylic acids, including anthranilic acid (AA) and salicylic acid (SA).[51] In a grinding competition experiment, sulfadimidine:SA cocrystal material was ground in the presence of single-component AA material, and subsequent analysis revealed that AA displaced SA as sulfadimidine's countermolecule to generate sulfadimidine:AA cocrystal material. The displacement may have been facilitated by the structural similarity of the two acid molecules, and the generality of this phenomenon requires further study. Nevertheless, a similarly designed grinding competition experiment might prophylactically assess the possibility of an analogous displacement occurring with a given cocrystal/excipient combination during formulation.

Non-Obviousness. Notwithstanding possible exceptions,[52] novel cocrystals are unlikely to be found unpatentable due to obviousness. The concept of obviousness is partly a legal determination, but with respect to crystal forms, obviousness can be analogized to the scientific notion of predictability. In 1988, the editor of the journal *Nature* suggested that the inability to predict a substance's crystal structure from its chemical structure was "one of the continuing scandals" of modern science.[53] Nearly two decades later, despite continuing advances in the field, the experimentally observable crystal form(s) of complex molecules such as APIs remain generally unpredictable.[54]

An intriguing report recently addressed crystallographers' ability to visually predict the experimentally observed crystal structure from among several computationally derived possibilities.[55] Test organizers selected two separate single-component organic molecules for the test, and participants (attendees at the 2005 Congress of the International Union of Crystallography) voted for the structure of each molecule that they predicted, based upon visual inspection, to represent the experimentally determined crystal structure. The results were surprising in that, in both cases, the "correct" structure received the fewest votes. While limited in scope, the study presents an appealing argument for the non-obviousness of

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(51) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, A. F. Selective Formation of Hydrogen Bonded Cocrystals between a Sulfonamide and Aromatic Carboxylic Acids in the Solid State. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2213−2216.

(52) See, e.g., Manual of Patent Examining Procedure § 2144.09 (U.S. Patent and Trademark Office, August, 2006): "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities", but "the presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds."

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(55) Day, G. M.; Motherwell, W. D. S. An Experiment in Crystal Structure Prediction by Popular Vote. *Cryst. Growth Des.* **2006**, *6*, 1985−1990.

crystal structures of organic compounds among those of ordinary skill in the art.

Beyond simple visual inspection, modern advances in computational methods allow researchers to generate thousands of plausible crystal structures for a given molecule and rank the structures on the basis of a variety of parameters, including free energy, density, and frequency of hydrogen-bond interactions. Nonetheless, reliable predictions of which structure(s) will actually crystallize in the laboratory remains a challenging area of ongoing research. The Cambridge Crystallographic Data Centre sponsors periodic "blind tests" that provide a rough measure of progress in the field of computational prediction of unknown crystal structures. The blind test molecules are simpler than typical APIs, limited by the number of molecules in the crystallographic asymmetric unit and the degree of molecular flexibility. In spite of these simplifications, the most recent test had few successful predictions.[56]

The studies described above involved predictions of crystal structures of single-component systems. Cocrystals present even greater challenges. Aspects of cocrystal prediction include (1) determining whether a given set of two or more molecular components will undergo cocrystallization; (2) identifying the primary intermolecular interactions, e.g., hydrogen-bond motifs, that will exist within a particular cocrystal structure; and (3) envisioning the overall packing arrangement in the resulting cocrystal structure. Chemical informatics may be helpful in certain respects. For instance, a proposed intermolecular hydrogen-bond motif may be evaluated for its robustness across all known crystal structures by searching the Cambridge Structural Database.[57] Predicting the overall packing is a task best suited for computational modeling, but few studies have directly addressed cocrystal prediction, an inherently complicated task on account of multiple molecules in the crystallographic asymmetric unit and numerous stoichiometric possibilities.[58] The initial concern—whether particular molecules will pair within a crystal lattice to form a cocrystal rather than crystallize independently as a physical mixture—is itself a formidable question. In addition to assessing the relative lattice energies of the possible product phases, other practical complications include predicting the observed cocrystal stoichiometry and whether additional components, such as solvent or water, may become incorporated in the structure during synthesis.[59,60] Beyond structure prediction, forecasting a particular cocrystal's physical properties is generally an unworkable task.

Considering the current challenges of cocrystal prediction, cocrystal synthesis is likely to remain within the realm of trial-and-error experimentation for the foreseeable future, thereby rendering cocrystals non-obvious from a general patentability perspective.

III. The Importance of Pharmaceutical Cocrystal Patents

As with patents on new molecular entities, patents on pharmaceutical cocrystals may be important to the pharmaceutical industry in a number of key respects.

Commercial Advantages. A research organization generally files a patent application covering the chemical structure of an API soon after recognizing its therapeutic utility, thereby guarding against another organization independently filing on the same molecule. Accordingly, claims covering the chemical structure of an API often represent the primary patent protection for a marketed pharmaceutical product. In certain cases, however, additional patent protection can be obtained by patenting novel solid forms of the API discovered in development.

The decision of when to initiate API solid-form screening can bear on future market exclusivity. If API solid-form screening is conducted at an early stage, an application covering commercially viable solid forms can be filed together with an application covering the API chemical structure. This approach safeguards against other organizations filing applications on the same solid forms or attempting to develop technology which circumvents the product's IP protection. Alternatively, certain benefits and risks can accompany later-stage API solid-form screening. The effort and expense of solid-form screening may be postponed until definitive identification of the preferred final form is required for development and/or regulatory purposes. In this scenario, the initial chemical-structure patent application may be followed by filings covering any newly discovered solid forms of the API, thus providing a solid-form patent portfolio encompassing all therapeutically important solid forms of the API, including polymorphs, hydrates, solvates, salts, and cocrystals. If the FDA-approved product involves one of the new solid forms in this portfolio, then patent protection of the solid form of the approved product may persist after the core chemical-structure patent expires, potentially leading to increased revenue and improved market position.

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(60) Friščić, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. Screening for Inclusion Compounds and Systematic Construction of Three-Component Solids by Liquid-Assisted Grinding. *Angew. Chem., Int. Ed.* **2006**, *45*, 7546−7550.

In practice, many factors influence whether the latter approach is desirable, or even possible, for a particular API in development. The following hypothetical example illustrates the interplay between solid-form innovation and API market advantage. Company X discovers and files a patent application covering the chemical structure of a promising new API that initially exists only as an unstable amorphous solid. Several years later, in the course of ongoing development work, company X discovers a stable crystalline dihydrate of the API and files a second patent application covering this novel structural improvement. Provided the API eventually reaches the market as the preferred dihydrate form, the dihydrate patent may remain in force when the chemical-structure patent expires, thereby providing a market exclusivity advantage for company X. But competing innovations can thwart this potential market advantage. Company Y could develop a technology for stabilizing the amorphous form of the API that was initially disclosed in the chemical-structure application, leading to a dosage form with enhanced bioavailability over the dihydrate. Company Y could potentially market this amorphous form upon expiration of the chemical-structure patent (and before expiration of the dihydrate patent). Additionally, company Z could discover a novel cocrystal of the API that exhibits certain enhanced physical properties, also permitting potential early market entry.

This hypothetical example underscores the importance of research involving solid forms of APIs. If a company wishes to capitalize on solid-form innovations involving its own novel API, the strategy must combine significant product improvements with exhaustive solid-form screening. As exemplified above, a single commercially viable solid form that is missed during the screen—and later discovered and patented by a competitor—can defeat the strategy.

Screening for solid forms is critical to ensure that the optimum form is carried forward in development and to minimize the likelihood of unexpected form conversion. The strategy described above, however, adds another dimension to the importance of solid-form screening technologies. On the basis of the large number and variety of potential cocrystal-forming countermolecules, screens for cocrystals may demand a particularly large degree of resources and sophistication. Improvements in screening methods, including informatics-based approaches and efficient experimental techniques, should provide value to the industry from both a scientific and economic perspective.

Patent Litigation. Cocrystals offer an apparent advantage over polymorphs or hydrates with respect to the legal doctrine of "inherent anticipation". A claimed invention is not novel if it was described in a prior publication; in such cases the publication is said to "anticipate" the claim. A publication can anticipate a claim even if it does not expressly describe the claimed invention, provided that the claimed invention is a necessary consequence of that which was described in the publication: this is the "inherent anticipation" doctrine. The *Schering v. Geneva* court case illustrated the extent of this doctrine in the pharmaceutical field.[61] The claimed invention in *Schering* involved loratadine, an antihistamine marketed by Schering Corporation as the drug Claritin. At issue was the validity of claims directed to descarboethoxyloratadine, a bioactive molecule produced by in vivo metabolism of loratadine.[62] The court held that claims to the loratadine metabolite as a new molecular entity were inherently anticipated by a prior patent that described administration of loratadine to a patient, since the metabolite necessarily resulted from this administration.[63]

While *Schering* involved a covalent modification of a pharmaceutical, it is not difficult to foresee its extension to noncovalent API modifications. In fact, such issues were at the heart of a recent case involving the HCl salt of paroxetine, an antidepressant marketed by SmithKline Beecham Corporation as Paxil.[64] Paroxetine HCl can be crystallized in either an anhydrate or a hemihydrate crystal form. SmithKline developed the hemihydrate form, which had superior stability; moreover, patent protection of the hemihydrate expired much later than patent protection of the anhydrate.[65] When the earlier patent covering the anhydrate expired, a competitor, Apotex Corporation, filed an abbreviated new drug application (discussed further below) indicating an intent to enter the market with generic anhydrate paroxetine HCl. Ensuing litigation centered on whether the generic anhydrate product would infringe SmithKline's claim to the hemihydrate.

At the district court level, one argument involved whether Apotex would induce "gastrointestinal infringement" of SmithKline's patent via conversion to paroxetine HCl hemihydrate in the stomachs of patients, but this issue was not resolved.[66] This argument paralleled that of an earlier case involving the cephalosporin antibiotic cefadroxil, in which alleged infringement was based upon crystal form conversion from a hemihydrate to a monohydrate upon ingestion; the decision in that case hinged in part on the difficulty of proving such in vivo infringement.[67]

In the most recent appeal involving paroxetine HCl, SmithKline argued that crystallization of the anhydrate necessarily resulted in some, albeit potentially undetectable, quantity of the hemihydrate crystal form.[68] The court agreed

(61) *Schering Corp. v. Geneva Pharmaceuticals Inc.*, 339 F.3d 1373, 1375 (Fed. Cir. 2003).
(62) Villani, F. J.; Wong, J. K. U.S. Patent No. 4,659,716 (Apr 21, 1987).
(63) Villani, F. J. U.S. Patent No. 4,282,233 (Aug 4, 1981).
(64) *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005).
(65) (a) Barnes, R. D.; Wood-Kaczmar, M. W.; Curzons, A. D.; Lynch, I. R.; Richardson, J. E.; Buxton, P. C. U.S. Patent No. 4,721,723 (Jan 26, 1988). (b) Christensen, J. A.; Squires, R. F. U.S. Patent No. 4,007,196 (Feb 8, 1977).
(66) *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011, 1014 (D. Ill. 2003). See also: *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306, 1321 (Fed. Cir. 2004).
(67) *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 1992 U.S. Dist. LEXIS 5799 (D.N.J. 1992); *Zenith Lab. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418 (Fed. Cir. 1994).

and furthermore held that the claim to the hemihydrate covered even undetectable amounts of this crystal form, therefore deciding that the generic anhydrate product would infringe. But in considering the validity of the SmithKline hemihydrate patent itself, the court held that even though it was not proven that the hemihydrate existed prior to its patenting, the claim to the hemihydrate was nonetheless inherently anticipated, and therefore invalid, since the method described in the earlier anhydrate patent would have necessarily resulted in some quantity of the hemihydrate crystal form.[69]

This broad interpretation of the inherent anticipation doctrine could, at least in theory, be used by an infringer to threaten the validity of any patent covering a hydrate or polymorph of a compound which had previously been studied. In contrast, cocrystals may be less vulnerable to this potential legal pitfall. Excluding water and other common solvents, cocrystal-forming countermolecules are not generally introduced to crystallization experiments when cocrystal formation is not intended. So although significant prior research may have been performed on a particular API, a subsequently discovered cocrystal may be less prone to inherent anticipation than other solid forms of that API. The counterions of salts should generally provide the same benefit. Deliberate supramolecular modification[70] of APIs may thus represent an opportunity to avoid uncertainty over patent invalidity based on the inherent anticipation doctrine.

On the other hand, the "gastrointestinal infringement" issue could render certain cocrystals less desirable than other API crystal forms from a patent perspective. As discussed above, particular cocrystals may be susceptible to dissociation in the presence of atmospheric moisture. Some caffeine cocrystals, for instance, converted to crystalline caffeine hydrate in the presence of water vapor.[38] It is at least conceivable that the same behavior might occur in the stomach. Hypothetically speaking, if crystalline caffeine hydrate was a patented composition of matter, then treatment of patients with a caffeine cocrystal could result in unavoidable gastrointestinal infringement of the caffeine hydrate patent.[67] At least until cocrystal dissociation behavior is better understood scientifically, concern over this aspect of pharmaceutical cocrystallization seems remote.

In general, one indication of the importance of API crystal form patents is the large number of recent and ongoing litigations pertaining to patents on polymorphs, hydrates, and salts of successful pharmaceutical products. The widespread, systematic application of cocrystallization to APIs is a relatively recent development, but as research escalates and improved cocrystal products arrive on the market, future patent disputes may also involve pharmaceutical cocrystals.

Regulatory Issues. In the above-mentioned dispute involving paroxetine HCl,[64] the generic company sought to market the anhydrate crystal form before patent protection on the marketed, regulatory-approved hemihydrate crystal form expired. The generic company gained regulatory approval for paroxetine HCl anhydrate by way of an abbreviated new drug application, or ANDA. The ANDA is a mechanism introduced by the Hatch−Waxman legislation to reduce the time and cost of regulatory approval for generic products by allowing generic companies to rely on the innovator's clinical trials. Despite this shortcut, regulators require a generic manufacturer to demonstrate that its product is the "same", for FDA purposes, as the originally approved product. According to the most recent FDA draft guidance,[71] a different polymorph or hydrate crystal form of an API may satisfy the "sameness" requirement for ANDA eligibility provided it exhibits comparable stability and bioequivalence.[72] In addition to paroxetine HCl, the FDA has approved other ANDAs involving alternate polymorphs (e.g., warfarin sodium, famotidine, and ranitidine) and hydration states (e.g., terazosin HCl and cefadroxil) of APIs.

Unlike polymorphs and hydrates, new salts of an API are generally ineligible for ANDA submission, instead requiring more extensive testing data for regulatory approval.[73] The most recent FDA draft guidance[74] maintains that a different salt form of an API constitutes a change in active ingredient, potentially necessitating the submission of additional clinical trial data (although, in certain cases, reference to previously published clinical data can be sufficient). The requirement of additional clinical studies introduces additional risk and expense for a generic company intending to market an alternative salt form of an approved product.

Pharmaceutical cocrystals, by contrast, have not yet been officially addressed from the perspective of generic regulatory approval. In some respects, cocrystals are intermediate between hydrates (which are ANDA-eligible) and salts (which, in general, are not). Like hydrates, cocrystals are nonionic supramolecular complexes; but like salts, cocrystals involve complexation with substances of greater potential toxicity than water. The issue of whether a new cocrystal of a marketed API may be eligible for regulatory approval via the ANDA mechanism will impact the overall utility of cocrystal technology to the generic pharmaceutical industry,

(68) *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005).

(69) This case may yet be reviewed by the U.S. Supreme Court; see: *SmithKline Beecham Corp. v. Apotex Corp.*, 126 S. Ct. 1133 (2006).

(70) Aakeröy, C. B. Crystal Engineering: Strategies and Architectures. *Acta Crystallogr*. **1997**, *B53*, 569−586.

(71) Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism. Food and Drug Administration Center for Drug Evaluation and Research; Draft Guidance, December 2004.

(72) Bioequivalence generally requires that the generic product exhibit no significant difference between the rate and extent to which the API becomes available to the site of drug action when administered under similar conditions to the innovator product. See: 21 C.F.R. § 320.1(e).

(73) See: 21 C.F.R. § 314.54.

(74) Guidance for Industry: Applications Covered by Section 505-(b)(2). Food and Drug Administration Center for Drug Evaluation and Research; Draft Guidance, October 1999.

and may possibly bear on the future marketplace abundance of pharmaceutical products containing cocrystals.

IV. Outlook

Cocrystallization is a flourishing research field with direct application to the pharmaceutical industry. Although the merits of each new invention must be evaluated on a case-by-case basis, pharmaceutical cocrystals generally appear patentable when measured against the criteria of novelty, utility, and non-obviousness. As part of a comprehensive solid-form patent portfolio, pharmaceutical cocrystals may offer a distinct commercial advantage with respect to market exclusivity. This potential advantage may be tempered, however, by the sizable burden of performing a thorough cocrystal screen and the risk that an extensive screen will nonetheless miss a viable cocrystal. In this regard, research that improves upon the ability to assess the cocrystallization potential of APIs will find immediate scientific and commercial utility. The value of cocrystals to the pharmaceutical industry should become clearer, particularly with respect to several relevant legal and regulatory issues, as products containing cocrystal technology emerge from pharmaceutical development pipelines onto the market.

Acknowledgment. Thanks to Mr. Anthony Insogna of Jones Day for critical review of the intellectual property aspects of this manuscript. Thanks to Dr. Bill Jones of the University of Cambridge and Dr. Sam Motherwell of the Cambridge Crystallographic Data Centre for instruction on scientific aspects of pharmaceutical cocrystals. Thanks to the Cambridge Crystallographic Data Centre for partnering with Jones Day to pilot the Cambridge Structural Database in a legal environment.

MP070001Z