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Potential Loss of 180-Day Exclusivity

by J. Mark Pohl

Introduction

In 1993, the United States Food and Drug Administration (FDA) approved Janssen Pharmaceutica N.V.'s New Drug Application (NDA) to market Risperidal brand risperidone in the United States.[1] Janssen listed several patents in the FDA's *Guide To Therapeutic Equivalents (Orange Book)*. One of these patents was United States Letters Patent No. 5,158,952, a patent claiming the 9-hydroxy salt of risperidone, and any "pharmaceutically acceptable acid addition salt thereof."

On August 28, 2001, Teva Pharmaceuticals filed an Abbreviated New Drug Application (ANDA) to market generic risperidone.[2] In it, Teva included the first filed "Paragraph (iv) Certification" against the '952 patent.

On April 18, 2008, the District Court for the District of Columbia issued an injunction compelling FDA to grant 180-day exclusivity to Teva.[3] The United States Court of Appeals for the District of Columbia Circuit, however, overruled the District Court and held that Teva was not entitled to a 180-day exclusivity period.[4]

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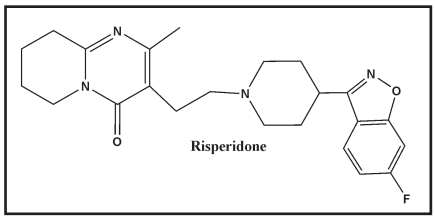

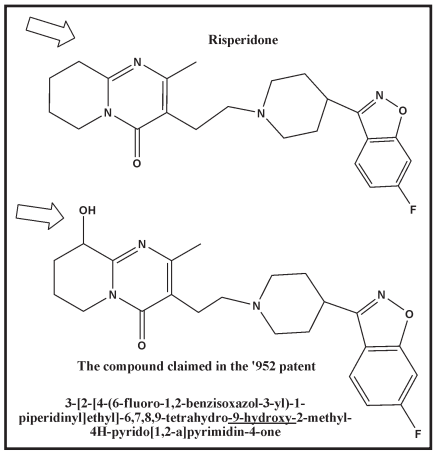

This article explains why the appeals court ruled the way that it did, and what opportunities this case poses for innovator and generic manufacturers. The author first assesses the patent at issue, and evaluates how it arguably might cover the drug at issue. To do this, the author presents a brief review the patent, and then compares it to Janssen's drug substance.

After assessing how the patent covers the innovator's drug substance, a review of the chronology of significant events from the approval of Janssen's NDA to the instant court cases is presented. This chronology sheds light on how the relevant law evolved over the period, and how the various generic risperidone manufacturers responded to this evolving legal landscape. The chronology concludes with an in-depth review of the rulings by FDA, the District Court, and the Court of Appeals.

After reviewing the various administrative and court rulings, the author posits several new opportunities this case provides for innovator manufacturers and for generic manufacturers.

The 9-Hydroxy Risperidone Patent

Risperidone, systemic name 4-[2-[4-(6fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-on, is an antipsychotic medication.[5] *See* FIGURE 1.

In 1992, Janssen obtained United States Letters Patent No. 5,158,952. The '952 patent literally claims "3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one":[6]

1. A compound selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, a pharmaceutically acceptable acid

addition salt thereof, and an enantiomeric form thereof.

This compound is not risperidone, but the 9-hydroxy form of risperidone.

Risperidone and 9-hydroxy risperidone differ because in risperidone, the basic hydroxyl moiety at the 9' position is replaced by an acidic hydrogen. *See* FIGURE 2.

The two structures differ by having an acidic hydrogen or a basic hydroxyl moiety at the 9' position. Janssen, however, listed the '952 patent in the FDA *Orange Book* as claiming risperidone. This indicates that, at least on the patent listing date, Janssen understood that its patent covered risperidone.

Janssen could reasonably have been arrived at this conclusion from either or both of two claim interpretations. First, risperidone differs from the 9-hydroxy form by replacing the basic hydroxyl moiety at the 9' position with an acidic hydrogen. In contrast, claim 1 of the listed patent literally covers not only 9-hydroxy risperidone, but also any "pharmaceutically-acceptable acid addition salt" of it. Janssen could thus have concluded that risperidone is a "pharmaceutically-acceptable acid addition salt" of 9-hydroxy risperidone. This interpretation would mean that claim 1 of the *Orange Book* listed patent reads on risperidone literally.

Alternatively, Janssen could have understood that risperidone is not significantly different from 9-hydroxy risperidone. In fact, the pharmaceutically active form of risperidone is 9-hydroxy-risperidone: risperidone is metabolized *in vivo* into the 9-hydroxy form. The 9-hydroxy form therefore would appear to have identical pharmacodynamics to risperidone; that is, it performs the same function as risperidone, in the same way, to produce the same clinical result. Janssen could therefore have reasonably concluded that risperidone is a legal equivalent of the literally claimed compound (9-hydroxy risperidone) and the '952 patent thus covers risperidone under the legal Doctrine of Equivalents.[7]

Another of Janssen's actions implies the equivalence of the two compounds. On November 30, 2005, Janssen applied for FDA approval to market 9-hydroxy risperidone. Janssen's NDA explains that both risperidone and the 9-hydroxy form are suitable for use in identical clinical indications. This indicates that Janssen believed that risperidone and the 9-hydroxy form were clinically similar, if not interchangeable.

Further, Janssen filed its NDA for 9-hydroxy risperidone under Section 505(b)(2) of the FDCA. Proceeding under Section 505(b)(2) intimates that Janssen believed that the clinical results obtained with risperidone do not conflict with the data which would be obtained with the 9-hydroxy form. Both of these factors imply that Janssen believed risperidone interchangeable with the 9-hydroxy form.

Given the fact that the patent literally covers acid addition salts, and given the fact that Janssen filed its NDA for 9-hydroxy risperidone under Section 505(b)(2) of the FDCA, one might reasonably infer that Janssen interpreted the '952 patent to read on risperidone. This interpretation would not appear at all unreasonable, in light of the plain language of the claim.

Janssen De-listed the Patent

FDA approved the risperidone NDA on December 29, 1993. On June 11, 2007, approximately two months before generic manufacturers could file ANDA applications, Janssen asked FDA to de-list the 9-hydroxy risperidone patent.[8] By July 20th, FDA had updated the electronic version of the *Orange Book* to show that the patent had been de-listed. FDA did not, however, update the paper version of the *Orange Book*.[9]

In August, both Mylan Laboratories[10] and Teva Pharmaceuticals (USA) filed ANDA applications for generic risperidone. Mylan, relying on the electronic version of the *Orange Book*, did not certify against the '952 patent in its ANDA.[11]

In contrast, Teva—ostensibly relying on the paper version of the *Orange Book*—included a "Paragraph (iv) Certification" against the 9-hydroxy risperidone patent in its own ANDA. Teva argued that because it was the first company to file a Paragraph (iv) certification against the 9-hydroxy risperidone patent, it should be awarded 180-day exclusivity. In October, FDA advised Teva that its ANDA was not acceptable because it contained a Paragraph (iv) Certification against a non-listed patent. FDA accordingly asked Teva to delete the 9-hydroxy risperidone patent Certification from its ANDA. Teva did so almost immediately, amending its ANDA to specify that it had been filed pursuant to Paragraph (iii), rather than Paragraph (iv). Teva said:[12]

"Revised patent certification. U.S. Patent 5,158,952 with an expiration of October 27, 2009 has been officially delisted from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), therefore only U.S. Patent 4,804,663 with an expiration of December 29, 2007 remains. Please find enclosed a patent certification revised accordingly. (Attachment 2)."

Six years after it had filed its ANDA, however, Teva changed position and petitioned FDA to re-list the '952 patent in the *Orange Book*.[13] As support, Teva argued that between the date it filed its

ANDA and the date it petitioned for re-listing, the law had changed.

To understand how the law had evolved over the several years, we need to review several key cases dealing with off-label uses and with a refusal by the innovator to sue an ANDA filer.

Off-Label Use : The Gabapentin Case

The first is the gabapentin case, *Purepac Pharmaceutical Co. v. Thompson*.[14] The gabapentin case was decided in January 2004, several years after Teva amended its risperidone ANDA to withdraw its Paragraph (iv) certification against the '952 patent.

FDA approved gabapentin for epilepsy. Pfizer, the innovator for Neurontin gabapentin, listed three patents in the *Orange Book*. One of the listed patents claimed the use of gabapentin to treat "neurodegenerative disease." Treating "neurodegenerative disease," however, is not an approved indication for the product labeling.

Purepac filed an ANDA, including Paragraph (iv) Certifications against the first two *Orange Book*-listed patents. In contrast, regarding the "neurodegenerative disease" patent, Purepac included a Section (viii) carve-out statement, stating that Purepac was not seeking approval for the unapproved off-label use.

A month later, TorPharm filed its own ANDA. Unlike Purepac, however, Torpharm included a Paragraph (iv) Certification against each and every one of the three listed patents—including the "neurodegenerative disease" patent. In so doing, TorPharm became the first ANDA applicant to file a Paragraph (iv) certification against the "neurodegenerative disease" patent. TorPharm thus would qualify for 180-day exclusivity.

Pfizer sued. During the patent infringement litigation, however, FDA asked Pfizer to voluntarily de-list the "neurodegenerative disease" patent from the *Orange Book*. Pfizer complied.

Because the "neurodegenerative disease" patent was no longer included in the *Orange Book*, FDA then required TorPharm to amend its ANDA to delete its Paragraph (iv) Certification against the "neurodegenerative disease" patent. By doing so, however, TorPharm became only the *second* filer (after Purepac) to certify against the two remaining listed patents. By so doing, TorPharm lost its 180-day exclusivity to Purepac.

One could interpret *Purepac* as standing for the proposition that an innovator can de-list a patent after filing suit, and such de-listing voids any 180-day exclusivity period based on that patent.

Alternatively, however, one could read *Purepac* as standing for the proposition that an innovator can de-list a patent after filing suit against an ANDA applicant if—but only if—*someone* retains the right to 180-days exclusivity. In other words, once a Paragraph (iv) Certification is made, a legal property right is created—a right to a 180-day exclusivity period; subsequent patent de-listings can perhaps cause that property right to spring from one ANDA applicant to another, but should not annul the property altogether.

Refusal to Sue: The Simvastatin Case

In the simvastatin case, *Ranbaxy Laboratories Ltd. v. Leavitt*,[15] the innovator listed three patents: one conventional utility patent and two reissue patents. Ranbaxy and Teva each filed a Paragraph (iii) Certification against the utility patent, and Paragraph (iv) Certifications against each of the two reissue patents. In response, the innovator voluntarily de-listed the reissue patents from the *Orange Book* without suing either generic manufacturer. The simvastatin case thus differs from the gabapentin case because in the simvastatin case, the innovator de-listed its patents *before* litigating, and indeed *never enforced* the de-listed patents.

The Court of Appeals concluded that Ranbaxy and Teva had earned their right to 180-day (co)exclusivity when they filed their Paragraph (iv) Certifications, and that once a right to an exclusivity period is created, the right does not vanish simply because the innovator later de-lists the patent at issue.

The outcome in *Ranbaxy* is at first glance more consonant with the second interpretation of *Purepac* discussed above. That is, once a Paragraph (iv) ANDA is filed, a patent can be de-listed only if *someone* retains the right to 180-days exclusivity. A patent de-listing can cause the right to 180-day exclusivity to spring from one ANDA applicant to another, but should not void the right to 180-day exclusivity period altogether.

Refusal to Sue: The Risperidone Case

In the risperidone case, Janssen asked FDA to de-list the '952 patent in 2001, before anyone had even filed an ANDA. Teva nonetheless included a Paragraph (iv) certification against the '952 patent in its subsequently-filed ANDA. When FDA identified the discrepancy, Teva immediately responded by amending its ANDA to delete its Paragraph (iv) Certification against the '952 patent.

Six years later, Teva Petitioned FDA to re-list the patent and grant it 180-day exclusivity as the first-filed ANDA with a Paragraph (iv) Certification against that patent. The basis of Teva's Petition is notable. Teva's Petition in effect tacitly assumes that The Court of Appeals' 2006 decision in the "failure to sue" (simvastatin) case (discussed above) tacitly overruled the same court's 2004 decision in the "off label indication patent" (gaba-

pentin) case. Indeed, Teva's legal brief in support of its Petition does not even mention the gabapentin case:[16]

"In November 2006, the D.C. Circuit ruled that the plain text of the FDCA prevented FDA from effectuating the delisting of a patent following the submission of a paragraph IV certification as to that patent. *Ranbaxy Laboratories Ltd. V. Leavitt*, 469 F.3d 120, 125-126 (D.C. Cir. 2006). The court struck down FDA's practice because it "change[d] the incentive structure adopted by Congress," by "deprive[ing] the generic applicant of a period of marketing exclusivity" after the generic substitute and undertaken the risk of infringing the patent by filing a paragraph IV certification. *Id*. at 126. The D.C. Circuit thus held that FDA's approach to delisting contravened the plain meaning of the FDCA, and invalidated FDA's practice under *Chevron* step one. *Id*."

The timing of Teva's Petition is also notable. Teva could have asked FDA to re-list the '952 patent in 2001, when Teva filed its ANDA, or when FDA first informed Teva that a Paragraph (iv) Certification against the '952 patent was improper.

Teva, however, refused to do so, waiting until a competitor (Mylan) was close to launching its own generic, a full six years after Teva agreed to amend its ANDA. Once it filed its petition, however, Teva treated the matter as quite time-sensitive: indeed, Teva did not even wait for the agency to decide the Petition, but went to Federal District Court asking for emergency relief against the agency.

FDA responded by pointing out that Teva had already agreed, on the record, that the 9-hydroxy risperidone patent was properly de-listed. FDA relied on Teva's own amendment to its ANDA, which explicitly says so. Teva's amendment to its ANDA says:[17]

"Revised patent certification. U.S. Patent 5,158,952 with an expiration of October 27, 2009 has been officially delisted from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), therefore only U.S. Patent 4,804,663 with an expiration of December 29, 2007 remains. Please find enclosed a patent certification revised accordingly."

FDA also argued in effect that Teva's six-year delay barred Teva's request under the doctrine of laches.

On April 18, the District Court issued and injunction compelling FDA to re-list the patent and grant Teva 180-days of exclusivity. FDA appealed. Teva launched its generic on June 30th.

On September 12th, the Court of Appeals for the District of Columbia Circuit vacated the injunction and mandated that Teva's exclusivity period—or, more properly, the remaining 106 days of it—be revoked. The reasons for the Court's decision are telling.

Taking Advantage of Agency Error

First, Teva argued that FDA failed to timely update the paper version of the *Orange Book* to reflect the de-listing of the patent. Teva argued that it was entitled to rely on the obsolescent paper version of the *Orange Book, even though Teva in fact knew the patent had been de-listed in the up-to-date electronic version*. The Court's reaction to Teva's plea betrays a well-deserved bit of sarcasm:[18]

1. JUDGE KAVANAUGH: Well, what if there is a mistake
2. in the [paper] list though?
3. MR. LEFKOWITZ: If there is a mistake —
4. JUDGE KAVANAUGH: You win if there is a mistake in
5. the [paper] list is your position, right?
6. MR. LEFKOWITZ: Absolutely, Your Honor. If the —
7. JUDGE KAVANAUGH: *Even if everyone knows, including*
8. *you, that it's a mistake.*
9. MR. LEFKOWITZ: Well, first of all, that's not the
10. case at issue here.
11. JUDGE KAVANAUGH: Right.

Common sense prevailed, and the Court rejected Teva's argument.

Evaluating Infringement Does Not Require Reading the Patent

One aspect of the case which patent lawyers will find interesting is that the parties adopted a novel theory of patent claim interpretation.

Hornbook patent law teaches that to assess whether a patent claim covers a product, one needs to read the patent claim, construe it, and compare the construed claim to the accused product, to ascertain if the accused product has each and every element of the claim.

In the risperidone case, however, FDA argued (and Teva did not strongly dispute) that one need not read the patent to determine what it covers. Rather, the parties argued that the coverage of a patent is determined not by the patent claims, but by whether or not the patent is listed in the *Orange Book*. FDA, for example, argued:[19] "The effect of the withdrawal of the patent was to render the patent unavailable as a basis for certification because the patent no longer 'claimed' the drug or use of the drug and patent information no longer had to be filed for it."

The Court of Appeals thus concluded, "as a practical matter, a patent claims a drug when the NDA holder says it does."[20] This approach may strike patent lawyers as innovative. It may seem even more so, when we consider that neither party made of record the '952 *patent*, nor

any of its *claims*, and that neither party in the entire proceeding *compared* the claims to the product at issue.

The issue of whether the '952 patent covers risperidone, however, was central to the parties' appeal, because the FDCA *requires* an innovator to list in the *Orange Book* any patent "with respect to which 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 product."[21]

Indeed, FDA itself argued that the Court of Appeals must not review the agency's decision regarding the award (or denial) of 180-day exclusivity, but the agency's decision *regarding the scope and coverage of the '952 patent*. FDA argued:[22] "(j)(5)(B)(iv). The FDA decision under review—that the '952 patent, which had been withdrawn by the NDA holder, did not claim the relevant drug and thus could not be the basis for Teva's paragraph IV certification—was reasonable."

This indicates that the parties both believed that the case turned on the substantive coverage of the '952 patent, and whether or not the '952 patent read on Teva's generic product.

The Hatch-Waxman Act Protects the Public, Not the Generic Industry

In reviewing the injunction against FDA, the Court of Appeals applied the conventional standard for granting injunctive relief. Injunctive relief requires a finding of irreparable harm (i.e., a loss which is qualitatively not remediable by monetary damages) in the absence of injunctive relief, that an injunction is in the public interest, and that that the balance of equities (including, for example, potential harm to third parties) tips in the favor of injunctive relief.[23]

In the risperidone case, the Court of Appeals found that the conventional standard for injunctive relief inherently weights *against* granting 180-day exclusivity *to any* generic manufacturer, due to at least two of the above factors.

First, the standard for injunctive relief requires evaluating the public interest. Here, The Court of Appeals implied that a 180-day exclusivity period inherently affronts the public interest because it limits the public's access to low-cost generics during the exclusivity period.

Second, injunctive relief requires evaluating potential harm to third parties. Here, the Court of Appeals implied that a 180-day exclusivity period potentially harms third party generic manufacturers by preventing them from launching their own generic products. Indeed, in the risperidone case, a third party (Mylan Laboratories) tried to intervene, arguing that awarding Teva exclusivity would interfere with Mylan's product launch.

Third, while the Court of Appeals did not address the issue, the loss of 180-day exclusivity may not create an "irreparable" non-financial loss justifying grant of injunctive relief.

In contrast, the Court of Appeals found nothing to support granting 180-day exclusivity. Rather, the Court pointedly seemed to ignore policy concerns such as encouraging the generic drug industry generally, over the long term, by rewarding specific patent-challenge efforts in the short term. The Court's discussion of the standards for injunctive relief intimates that the Court has significant reservations with enforcing 180-day exclusivity equitably, not merely for risperidone, but for any Paragraph (iv) generic product.

A critical open question involves the effect of authorized generics on the Court of Appeals' calculus in assessing exclusivity periods. In the risperidone case, the Court of Appeals voiced a strong belief that Hatch-Waxman is intended to benefit *the public*, not *the generic industry*. To that end, the Court seems to want to assure that *the public* benefits by having access to inexpensive generics, rather than having *a specific generic manufacturer benefit* with 180-day exclusivity.

Neither the gabapentin case, nor the simvastatin case, nor the risperidone case involved authorized generics. A critical open question is, if the innovator launches an authorized generic product, would the Court of Appeals defend 180-day exclusivity if the relevant patents are de-listed before litigation (as in the simvastatin case), or perhaps even *after litigation has commenced* (as in the gabapentin case)? The Court's commentary during the risperidone case intimates that once there is a low cost generic supply from *some* source in the marketplace, the Court may not be particularly interested in equitably enforcing 180-day exclusivity to benefit any one generic manufacturer.

Summary

The Court's treatment of the parties' arguments provide important guidance to innovators and generic manufacturers on how to best address the Court's concerns regarding 180-day exclusivity.

1 *See Approval History for New Drug Application No. 020272* at Supplement No. 00 (29 Dec. 1993).

2 *See* Buehler, Gary, *Letter to Teva Pharmaceuticals USA, Inc. Regarding Abbreviated New Drug Application No. 076228* (June 30, 2008).

3 *See* Teva Pharmaceuticals USA, Inc. v. Leavitt, docket no. 1:08-cv-000395-RCL (D.D.C.) at *Order* (Apr. 11, 2008).

4 *See* Teva Pharmaceuticals USA, Inc. v. Leavitt, Appeal No. 08-5141 (D.C.Cir.) at *Judgment* (Sept. 12, 2008).

5 *See e.g.*, http://en.wikipedia.org/wiki/Risperidone (accessed Sept. 10, 2008).

6 *See* Janssen, Cornelius G.M. et al., *3-[2-[4-(6-fluoro-1,2-benzisoxozol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9 tetrahydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one, compositions and method of use,*

United States Letters Patent No. 5,158,952 (Oct. 27, 1992) at 20:36 *et seq.*

7 *See* Warner-Jenkinson Co. v. Hilton Davis Chemical Co., 520 U.S. 17 (1997) (a structure which differs "insubstantially" from the literally claimed structure may be legally equivalent to it); Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605 (1950) (a structure which performs the same function as the literally-claimed structure, in the same way as the literally-claimed structure, to produce the same result as the literally-claimed structure, is legally equivalent to it).

8 See e.g., Defendant's Memorandum In Opposition to Plaintiff's Motion for a Preliminary Injunction, Docket No. 08-cv-0395 (D.D.C.) at page 2 (Mar. 14, 2008).

9 *See e.g., Plaintiff's Memorandum In Support of its Motion for a Preliminary Injunction*, Docket No. 08-cv-0395 (D.D.C.) at page 12 (Mar. 4, 2008).

10 *See* ANDA No. 76-288 (Aug., 2007).

11 *See Mylan Pharmaceuticals Inc.'s Opposition to Teva's Motion for a Preliminary Injunction* (Mar. 26, 2008), docket no. 08-cv-395 (D.D.C.) at page 6.

12 *See* Jaskot, Deborah A., *letter to Gary Buehler regarding ANDA # 76-228* (Oct. 22, 2001).

13 *See* Jaskot, Deborah A., *Citizens Petition No. 2007P-0316* (Aug. 3, 2007).

14 United States Circuit Court of Appeals for the District of Columbia Circuit, Purepac Pharmaceutical Co. v. Thompson, Order in Appeal No. 02-5410 (Jan. 20, 2004).

15 United States Circuit Court of Appeals for the District of Columbia Circuit, Ranbaxy Laboratories Ltd. v. Leavitt, Order in Appeal No. 06-5154 (Nov. 14, 2006).

16 *See* Jaskot, Deborah A., *Citizens Petition No. 2007P-0316* (Aug. 3, 2007) at page 3.

17 *See* Jaskot, Deborah A., *letter to Gary Buehler regarding ANDA # 76-228* (Oct. 22, 2001).

18 United States Circuit Court of Appeals for the District of Columbia Circuit, Teva Pharmaceuticals USA, Inc. v. Leavitt, Appeal No. 08-5141, transcript of oral argument at page 14, lines 1-11 (Nov. 14, 2006).

19 United States Circuit Court of Appeals for the District of Columbia Circuit, Teva Pharmaceuticals USA, Inc. v. Leavitt, Appeal No. 08-5141, *Brief for the Appellants* at page 3 (June 18, 2008).

20 Teva Pharmaceuticals, USA, Inc. v. Leavitt, 548 F.3d 103, 106 (D.C.Cir. 2008).

21 *See* 21United States Code § 355(b)(1).

22 United States Circuit Court of Appeals for the District of Columbia Circuit, Teva Pharmaceuticals USA, Inc. v. Leavitt, Appeal No. 08-5141, *Reply Brief for the Appellants* at page 1 (Aug. 1, 2008).

23 E.g., The Supreme Court of the United States, Winter v. Natural Resources Defense Council, Order in Appeal No. 07-1239 (Nov. 12, 2008).