Using FDA's Citizen Petition Process and Litigation to Achieve Market Success

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Topics

- Overview of FDA's Citizen Petition process
- Market exclusivities and other issues that can be addressed in a petition
- Recent court decisions involving FDA issues
  - Maximizing your chance of success before FDA
  - To sue or not to sue FDA
  - Strategies for prevailing in Court against FDA

Citizen Petition Process

- First Amendment's Right to Petition
- Administrative Procedure Act, 5 U.S.C. § 533(e)
- FDA's regulations on petitions at 21 C.F.R. Part 10

- Any person may submit a citizen petition to FDA requesting that the agency
  - Issue, amend or revoke a regulation or order; or
  - Take or refrain from taking (staying) any other form of administrative action.

Recent Petition Trends

- Increase in petitions generally over last decade
  - 1998 OIG Report (~ 96 petitions/year)
  - FDA's current figure (~ 200 petitions/year)

Year	Drug Petitions
2001	10
2002	17
2003	16
2004	32
2005	19
2006	32
2007	30
2008	32
2009	37
2010	33

- Uptick in petitions related to drugs over last decade, with number of petitions fairly constant over the past few years*

* Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 Cardozo L. Rev. 249 (2012); FDA's Annual Reports to Congress on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for FYs 2008-2012.

Sec. 505(q) of FDAAA

- Food and Drug Administration Amendments Act (FDAAA) enacted in Sept. 2007
  - Added Section 505(q) to the FDCA
  - Result of sharp rise in drug-related citizen petitions and corresponding backlog
- Section 505(q) applies to petitions requesting FDA to take any form of action related to a *pending* ANDA, 505(b)(2) or biosimilar application
  - Approval of pending application should not be delayed due to the petition unless a delay is necessary to protect public health
- Number of 505(q) petitions filed annually has remained steady since FDAAA (Fifth Annual Report to Congress)

Impact of FDASIA

- Section 1135 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) shortens the deadline for FDA to respond to 505(q) petitions from 180 days to 150 days.
- Latest Report to Congress: Represents a significant shortening of time for FDA to evaluate the petition's issues and formulate a response; resulted in a redirection of resources from other initiatives
- Impact – more non-substantive responses
  - Recent examples: Rejections within 150 days because issues were still premature, and FDA would like to review future ANDA data before deciding on these issues

Issues to Address With Citizen Petitions

- Petition FDA to issue, amend, or revoke an order or regulation
  - e.g., bioequivalence guidelines; labeling requirements; regulations governing approval, exclusivity,* and forfeiture.
- Petition FDA to take or refrain from taking certain administrative actions
  - e.g., approve a drug product; grant or revoke exclusivity* for a drug product; grant or deny approval of a drug product

*Different types of exclusivities:

- Orphan Drug: 7 years
- New Chemical: 5 years
- "Other" Exclusivity: 3 years for a "change" if criteria are met
- Pediatric Exclusivity: 6 months added to existing exclusivity
- Patent Challenge: 180 days

Recent Court Decisions Involving FDA Issues

1. Tentative approval requirements and loss of 180-day exclusivity for failure to obtain tentative approval (valganciclovir and esomeprazole)
2. Effect of reissue patent on first filer's eligibility for 180-day exclusivity (celecoxib)
3. Acceptability of *in vitro* bioequivalence data for highly soluble locally acting drugs; eligibility for additional three-year exclusivity period based on labeling amendment not referencing a new indication or condition of use (vancomycin)

Valganciclovir & Esomeprazole

Main issue

– Whether tentative approval ("TA") of applicant's proposed generic product is appropriate when the applicant cannot demonstrate present compliance with current good manufacturing practices (cGMPs) at the sites where the product is to be manufactured.

Valganciclovir & Esomeprazole

Timeline

- 2006: FDA grants "TA" to Ranbaxy for valganciclovir despite ongoing compliance problems with cGMPs and data integrity concerns.
- 2012: FDA completes audit and finds no data irregularities; cGMP compliance issues persist.
- 2014 (February) Endo asks FDA to revoke Ranbaxy's 180 day exclusivity – controlled correspondence.
  - Ranbaxy was never eligible for TA in the first instance due to ongoing cGMP compliance issues. Accordingly, 180 day exclusivity should be revoked because Ranbaxy failed to receive TA within 30 months of filing.
- 2014 (May): Dr. Reddy's submits citizen petition.

Valganciclovir & Esomeprazole

Timeline (November 2014)

- FDA issues Letter Decision revoking Ranbaxy's TA and 180-day exclusivity.
  - FDA erred in granting TA when Ranbaxy's cGMP compliance status was in doubt. Revoked TA because it never should have been granted in the first place.
  - Ranbaxy no longer eligible for 180-day exclusivity because it failed to obtain TA within 30 months of submitting its ANDA.
- FDA grants final approval to Dr. Reddy's and Endo.
- Ranbaxy files complaint against FDA in the District of D.C. and moves for temporary restraining order and preliminary injunction.
- Endo and Dr. Reddy's intervene as defendants on the side of FDA.

Valganciclovir & Esomeprazole

Ranbaxy's Motion for TRO/PI

- Ranbaxy asserted that TA merely requires a blueprint for eventual compliance with cGMPs rather than present ability to comply with cGMPs.
- Ranbaxy also asserted that once TA is granted, FDA does not have authority to revoke.
- Accordingly, Ranbaxy argued that FDA's decision to revoke TA based on Ranbaxy's compliance issues was arbitrary and capricious

Valganciclovir & Esomeprazole

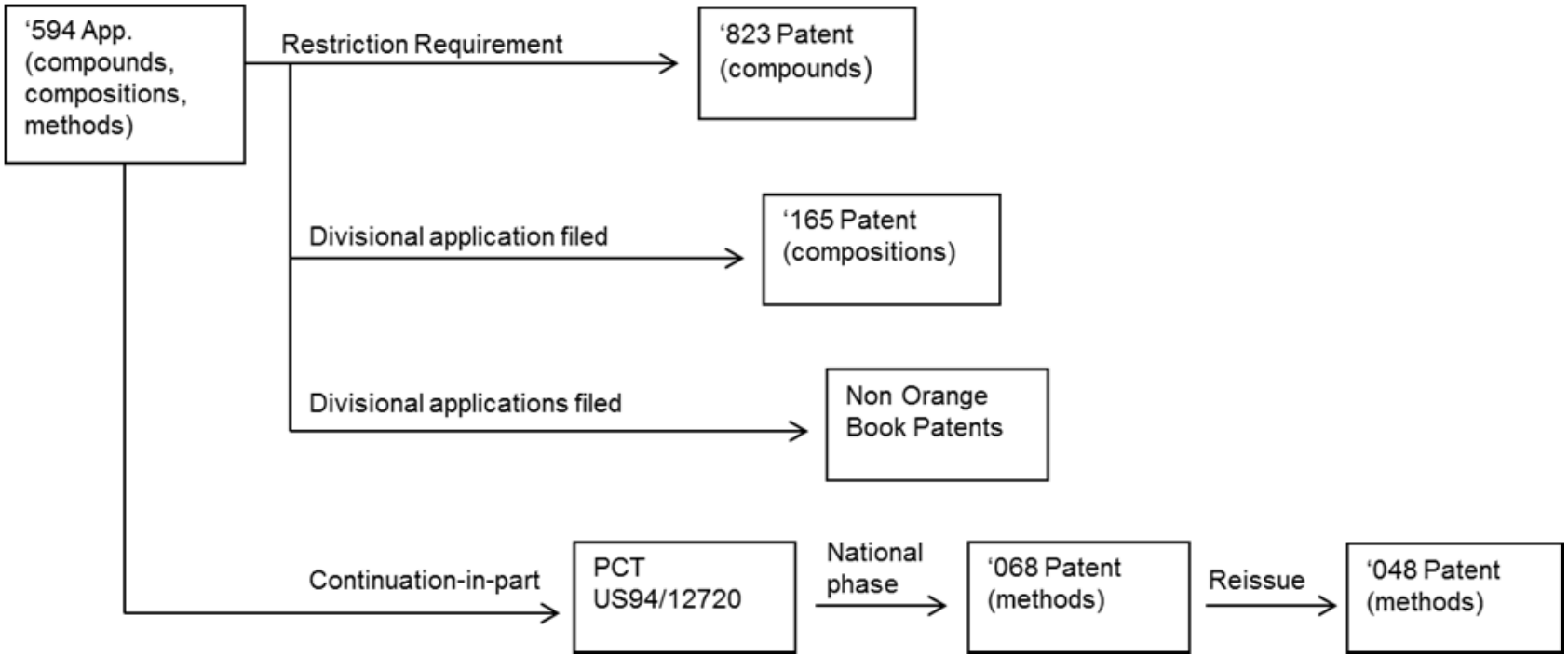
Hearing on Ranbaxy's Motion for TRO/PI

- Irreparable harm:
  - At the time of the hearing, the OB valganciclovir patent was set to expire in 4 months.
  - Ranbaxy made no showing as to if and when it expected to receive final approval.
- Likelihood of success on the merits:
  - Court deferred to FDA's reasonable interpretation of ambiguous TA provisions.
  - Ranbaxy's interpretation placed "form over substance" and would lead to results contrary to the purpose of the Hatch-Waxman framework
- Balance of hardships:
  - Court did not emphasize this factor, but was not sympathetic to the fact that defendant-intervenor Endo would be greatly harmed because it went to market with generic product the day before the TRO hearing.
- Public Interest:
  - The public benefits from low-cost generic drugs.

Celecoxib

Main Issue

– Whether the Hatch-Waxman Act treats reissued patent(s) as separate and distinct from the original patent(s) for the purpose of determining an ANDA filer's eligibility for 180-day exclusivity.



Celecoxib

Timeline

- 2003: Pfizer produces Celebrex (celecoxib), protected by the '823, '165, and '068 patents; Teva files ANDA containing Paragraph IV certifications to the '823, the '165, and the '068 patents; Pfizer sued Teva for patent infringement.
- 2007: District Court for District of N.J. found patents valid and infringed.
- 2008: Federal Circuit reversed in part, deeming claims of the '068 patent invalid.
- 2009: Mylan, Watson, and Lupin filed ANDAs for celecoxib containing Paragraph IV certifications.

Celecoxib

Timeline (2013-14)

- USPTO reissues the '068 patent as RE44,048 ("the '048 patent").
- Mylan, Watson, and Lupin file Paragraph IV certifications to the '048 patent and petition FDA regarding eligibility for 180 day exclusivity based on status as first filers to the reissued patent.
- E.D. Va. finds '048 patent invalid.
- After hearing from impacted parties, FDA issues Letter Decision concluding that original and reissued patents provide a "single bundle of patent rights," and thus a reissued patent cannot be the basis for a new period of 180-day exclusivity.
- Mylan filed suit against FDA in N.D. W.Va. seeking injunctive and declaratory relief regarding FDA's letter decision; Watson and Lupin intervened as plaintiffs, and Teva intervened as a defendant.

Celecoxib

District Court

The district court consolidated the hearing on Plaintiffs' preliminary injunction motion with a trial on the merits. The court granted judgment in favor of FDA and dismissed the case. Plaintiffs appealed.

- Likelihood of success: Court deferred to FDA's "bundle of patent rights" approach to determining exclusivity.
- Irreparable harm: Court emphasized that economic harm from delayed entry to market does not by itself entitle Plaintiffs to preliminary injunction.
- Balance of hardships: Court stated that Teva's loss of sole exclusivity would be at least as harmful as Plaintiffs' loss of shared exclusivity.
- Public interest: Awarding exclusivity to the first ANDA filer to risk being sued for infringement (in this case, Teva) incentivizes companies to bring generic drugs to market and therefore benefits the public.

Celecoxib

Court of Appeals for the Fourth Circuit

- FDA's interpretation fails at Chevron step 1 because Congress clearly and unambiguously spoke to the issue.
- Although the Hatch-Waxman Act does not define "patent" or mention reissued patents, the statute is not ambiguous regarding exclusivity triggers.
  - Congress spoke directly to the issue, clearly stating that 180-day exclusivity runs from "the date of a decision of a court in an action . . . holding the patent which is the subject of the certification to be invalid or not infringed." 21 U.S.C. § 355(j)(5)(B)(iv).
  - Court decision trigger speaks of "the patent which is the subject of the certification" 21 U.S.C. § 355(j)(5)(B)(iv).

Celecoxib

Court of Appeals for the Fourth Circuit

- The 2008 Federal Circuit decision triggered an exclusivity period regarding the '068 patent; Teva's marketing of celecoxib would not infringe the original patent.
- The '048 reissue patent, however, represented a new set of rights granted by the PTO, thus necessitating new Paragraph IV certifications and a new legal challenge to determine validity.

"The plain language of the statute indicates that each patent that is the subject of a certification may trigger exclusivity. . . [b]ecause we find that FDA's interpretation to the contrary violated the plain statutory language, we must set it aside."

Vancomycin

Main Issues

- Whether a label change for Vancocin (vancomycin) reflecting new clinical data but providing no new indication or condition of use renders the drug eligible for additional three years of statutory exclusivity under 21 U.S.C. § 355(j)(5)(F)(iv).
- Whether FDA has the discretion to accept either *in vivo* or *in vitro* bioequivalence data from generic applicants or there is a default requirement to show bioequivalence through *in vivo* testing.

Vancomycin

Timeline

- 2004: ViroPharma receives exclusive license to market vancomycin in the U.S.
- 2006: Generic drug manufacturers tell FDA that because vancomycin acts locally in the GI tract, it is nearly impossible to do *in vivo* bioequivalence study.
  - FDA had previously recommended that generic applicants provide *in vivo* data, but changes recommendation to permit applicants to establish bioequivalence through *in vitro* dissolution studies.
  - ViroPharma files citizen petition to stay approval of any vancomycin ANDA relying on *in vitro* dissolution studies.
- 2009: FDA Advisory Committee endorses *in vitro* dissolution studies for showing bioequivalence of generic vancomycin products

Vancomycin

Timeline (continued)

- 2011:
  - ViroPharma files supplemental NDA for a label change reflecting new clinical data (but no new indications or conditions of use).
  - ViroPharma amends citizen petition to include claim for three-years of additional exclusivity based on this label change.
- 2012:
  - FDA denies ViroPharma's exclusivity and bioequivalence claims in a comprehensive letter ruling.
  - FDA approves ANDAs for vancomycin submitted by Akorn, Alvogen and Watson.
  - ViroPharma files suit against FDA in District of D.C. and moves for preliminary injunction to require FDA to withdraw ANDA approvals.

Vancomycin

District Court TRO/ PI Hearing

- Likelihood of success: Court found that Hatch-Waxman new label exclusivity and bioequivalence guidelines are ambiguous, so deferred to FDA's reasonable interpretation based on the agency's evaluation of scientific data within its area of expertise.
- Irreparable harm: Court emphasized that economic harm from increased competition is not enough by itself; reputational injury from potentially unsafe generic products is too speculative.
- Balance of hardships: Court found this factor weighed clearly in defendant-intervenors' favor, as their products had already hit the market.
- Public interest: Court found that this factor favored defendant-intervenors, as the public benefits from increased access to generic drugs.

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Any Questions?

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