

Citizen Petitions Are Crucial In Managing A Drug's Life Cycle

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A citizen petition is a tool for petitioning the government which, properly applied, can be used to:

1. Advance the goal(s) of a pharmaceutical company;
2. Gain advantage(s) against a competitor (branded or generic); or
3. Alert the U.S. Food and Drug Administration of a potential public health hazard.

These objectives need not be mutually exclusive. Although we focus here on drugs — prescription and over-the-counter — citizen petitions have been used in other regulated categories such as dietary supplements.

With creativity, clear objectives and a thorough understanding of underlying facts and issues, citizen petitions may be useful with regard to other regulated products, such as: foods including medical foods; medical devices including diagnostic tests; human cells, tissues and cellular and tissue-based products; cosmetics; and radiation emitting devices.

Extending Pharmaceutical Market Exclusivity

We define good life cycle management as the use of all legally available tools to (1) maintain drug franchise exclusivity in the market and (2) maximize revenue from sale of the drug.

For many types of drugs, including drugs approved for treating chronic illnesses, drug sales and revenue tend to increase markedly over the drug's life. This means that revenues towards the end of a drug's market exclusivity period can be significantly greater than revenues generated earlier in time. Good life cycle management aims to extend the valuable near-end period of drug market exclusivity.

As one tool in the life cycle management toolbox, citizen petitions may be used to extend drug market exclusivity. Citizen petitions may be employed by themselves, but are often used in conjunction with other tools including: patents, Orange Book listings, dosing and



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formulation changes, labeling revisions, regulatory exclusivities, risk evaluation and mitigation strategies, drug reformulation and transitioning patients from one dosage form to another; to prolong a drug's market exclusivity.

Common Citizen Petition Requests

For prudent life cycle management, pharmaceutical companies often request that the FDA take at least one of the following acts (this list is not exhaustive):

- Deny a biowaiver to a generic drug applicant.
- Require one or more clinical studies of a generic applicant prior to approval.
- Require conducting a clinical trial on a targeted patient population.
- Ask for a bridging clinical study.
- Necessitate a food effect clinical study.
- Require a comparative demonstration of nonclinical superiority.
- Prohibit approval pathways alternative to those previously established.
- Demonstrate no absorption or efficacy effect from a formulation ingredient.
- Require recall one or more drugs.
- Declare a moratorium on future approvals of a drug or drug class.
- Withdraw a guidance.
- Issue a new guidance.
- Show bioequivalence between a salt and nonsalt form of a drug.
- Show bioequivalence between two drug polymorphs.
- Change the therapeutic equivalence rating of a drug.
- Require bioequivalence data of a parent compound and a metabolite.
- Require determination of additional bioequivalence parameters.
- Require an immunogenicity study.
- Designate a reference listed drug.
- Set a required level of "sameness" between a branded drug and a proposed generic.



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- Require impurity characterization, identification and safety confirmation.
- Require specialized stability analysis.
- Award a longer period of regulatory exclusivity.
- Award a further period of regulatory exclusivity.
- Require bioequivalence data of a parent compound and a metabolite.
- Require additional bioequivalence parameters.
- Confirm that a discontinued drug was not discontinued for reasons of safety and efficacy.
- Overturn another citizen petition decision.
- Require that all labeling for a drug, whether branded or generic, contain specific language relating to safety and efficacy.

An example of the last item described above is found in a citizen petition related to the drug sodium oxybate (Xyrem). A citizen petition was used in conjunction with clinical trial data, patenting, Orange Book listing, labeling changes and pediatric exclusivity, to extend Xyrem's market exclusivity. We briefly describe this approach below, with a focus that — for clarity and conciseness — excludes risk evaluation and mitigation and pediatric exclusivity-related life cycle management actions.

Sodium Oxybate

As described in their 2016 citizen petition, Jazz Pharmaceuticals Inc. conducted a clinical study in 2012 that uncovered a potentially harmful drug-drug interaction that occurs between Jazz's drug Xyrem and the drug divalproex sodium when these drugs are co-administered. Interaction between the two co-administered drugs resulted in a 25% mean increase in systemic exposure to Xyrem.

After discovering this interaction, Jazz obtained patent protection (example) based on their clinical trial discovery of the drug-drug interaction and convinced the FDA to approve Xyrem's revised labeling. The revised labeling included the following dosing provisions:

For patients already stabilized on Xyrem, it is recommended that additional divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose when introducing Xyrem.

Jazz listed its new drug-drug interaction patents in the Orange Book, which extend to 2033 (years after other Orange Book-listed patents would have expired). The patent claims tracked Xyrem's revised labeling. If a generic copied the drug-drug interaction language from Xyrem's label in the generic drug label, then Jazz was in position to assert these drug-drug interaction patents against the generic.

To avoid this infringement trap, several generics attempted to carve out the relevant drug-drug interaction language from their generic drug labels. Jazz's citizen petition, in part, asked the FDA to prevent these carveouts. Specifically, the citizen petition requested that the FDA refuse "to approve any

sodium oxybate [generic drug application] that does not include in its proposed labeling the portions of the Xyrem package insert related to divalproex.”

The FDA approved Jazz’s petition with respect to the drug-drug labeling carve out on Jan. 17, 2017, which informed the ongoing district court litigation and subsequent settlements.

Broader Citizen Petition Impacts

Citizen petitions can profoundly impact the public’s access to drugs, pharmaceutical companies that develop and commercialize those drugs, and can have broad ramifications that unfold over time. A recent impactful example of which nicely outlines the broad and ongoing ramifications a citizen petition can have is Valisure’s citizen petition — filed earlier this year.

Valisure’s Citizen Petition

According to the company’s website, Valisure was established after one of its founders “suffered serious complications caused by batch variability of his anticonvulsant medication.” Valisure is “dedicated to preventing anyone from suffering adverse effects from low quality medications.”

Valisure recently filed a citizen petition with the FDA. The citizen petition requests, among other things, that the FDA “recall and suspend all lots of all products containing ranitidine” because of the “drug’s propensity to form the probable carcinogen [N-nitrosodimethylamine].”

The petition describes that the antacid ranitidine, commonly sold under the brand name Zantac, is heavily prescribed to adults and infants, and sold over the counter, due to “a very high perception of safety.” Ranitidine has been marketed for decades.

Valisure’s petition further recites finding “extremely high levels of ... a probable human carcinogen [NDMA], in every lot tested, across multiple manufactures and dosage forms.” The petition states that the FDA has established a permissible daily NDMA limit of 96 ng, and that “Valisure has detected NDMA in excess of 3,000,000 ng per tablet when analyzing ranitidine products.”

The concerns raised by Valisure’s citizen petition were highly publicized by both the FDA and the press. Fallout from Valisure’s citizen petition continues. For example, companies including Sanofi and Dr. Reddy’s, Apotex and GalxoSmithKline, have all instituted drug recalls, which will likely impact drug revenue streams in major markets.

And mass tort lawyers are now advertising for potential plaintiffs who may have developed cancer as a result of taking ranitidine. But there are a number of potential ramifications from citizen petitions that are worth noting.

Citizen Petitions and Their Impact

Citizen’s petitions are published. Citizen petitions, however, may be redacted to preserve confidential information. Citizen petitions can be read by competitors, interested citizens, suppliers, creditors, healthcare professionals, shareholders, plaintiff’s lawyers, boards, employees, potential acquirers, the press and even Congress.

Information or data in a citizen petition can impact the public’s perception of a company and its

product(s), company stock price and valuation, and sales and revenue. Citizen petition filing(s) can trigger plaintiff's lawsuits, such as mass tort and shareholder lawsuits. Citizen petitions can also reshape a regulatory landscape, impacting approvals, approval timings and market exclusivities.

A well-crafted citizen petition can be used to enlist the full power and authority of the federal government to move against a company and its product(s), which could include criminal prosecution.

The content of citizen petitions can be immune from antitrust liability. This antitrust immunity is not absolute, and may not apply if the petition is determined to be a sham petition that is objectively and subjectively baseless.

Citizen petitions have a low submission threshold, which can encourage multiple and creative submissions. They can create demand shifts within targeted and adjacent markets. They can impact a company's — and even an industry's — relationship with the FDA and the federal government.

Conclusion

Citizen petitions, used alone and in conjunction with other tools as part of good life cycle management, can potentially extend a branded drug's market exclusivity. Citizen petitions can in some instances also initiate broad and ongoing ramifications, which can have worldwide impact on the availability of drug products. Good life cycle management, when appropriate, should include judicious use of citizen petitions.

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