UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	**)**	**MDL No. 1:15-md-2657-FDS**
	)	This document relates to:
	)	All Actions

PLAINTIFFS' MEMORANDUM CONCERNING GSK'S CITIZEN PETITION AND REQUEST FOR IMMEDIATE RELIEF OF THE RODRIGUEZ TRIAL DATE AND PRETRIAL DEADLINES

I. INTRODUCTION

On November 1, 2019—two business days prior to the scheduled oral argument on GSK's Renewed Motion for Summary Judgment Based on Federal Preemption—GSK filed a Citizen Petition with the FDA. (The FDA has assigned this petition ID number FDA-2019-P-5151-0001.) GSK's Citizen Petition is unlike most petitions submitted to the agency; it does not seek to have the agency "issue, amend, or revoke a regulation" or an agency "order." *See* 21 C.F.R. § 10.30(b)(3). Nor does it ask the FDA to consider the most recent scientific and regulatory developments concerning Zofran. *See* Citizen Petition at 1 ("This petition does not address . . . newly available epidemiological studies and an assessment of Zofran's labeling by the Pharmacovigilance Risk Assessment Committee (PRAC)."). Rather, GSK's petition merely asks the agency to opine on the relevance of "four other categories of information" to "Zofran's pregnancy-related labeling"—specifically, the four categories of information Plaintiffs have identified as withheld from the agency in its prior reviews of Zofran's pregnancy-related labeling. The Petition asks the FDA to take whatever action "the Agency deems appropriate" based on this specific information and, "[i]f the Agency deems it appropriate to alter the labeling," to "inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision." *Id.*

The Court has asked the Parties to submit memoranda addressing the implications of GSK's Citizen Petition for the pending renewed summary judgment motion, and Plaintiffs hereby submit this response. GSK's Petition represents a blatant misuse of the Citizen Petition process and Plaintiffs will shortly be filing comments with the FDA seeking dismissal of the petition. Moreover, its filing, on the eve of oral argument on the pending motion, reflects a clear intent on

GSK's part to interfere with this Court's consideration of the relevant legal issues concerning preemption and an inappropriate attempt to shift the authority to decide those issues from this Court to an executive branch agency in derogation of this Court's authority under Article III of the United States Constitution.

Additionally, it is clear that GSK has had multiple undisclosed communications with FDA officials concerning this matter, which should have been disclosed to Plaintiffs pursuant to existing discovery requests. At a minimum, Plaintiffs must be given an opportunity for full discovery concerning all such communications with the FDA and Novartis before this Court would take account of any FDA response to the Citizen Petition. Moreover, GSK has failed to provide the FDA with a full record of relevant documents concerning the "four other categories of information;" if the FDA declines to dismiss the Citizen Petition, Plaintiffs will be obliged to submit comments to the Agency in order to supplement the record (including numerous documents that GSK currently seeks to protect as confidential pursuant to the protective order). In any event, and of most immediate relevance to this Court, any action taken by the FDA in response to the petition will not be formal agency action with the force of law that would have binding preemptive effect on this Court; at most, an FDA response will amount to "agency musings" about what the agency would have hypothetically done if this information had been provided at the time of the FDA's earlier considerations of Zofran's pregnancy labeling. As both the majority opinion in *Merck Sharp & Dohme Corp. v. Albrecht* and Justice Thomas's concurrence make clear, such "agency musings" and "hypothetical agency action" are not law, and do not carry preemptive effect.

Plaintiffs nevertheless request this Court delay the Rodriguez trial until March 30, 2019, and similarly extend the pretrial scheduling order deadlines set out in this Court's October 17,

2019 Order, in light of GSK's Citizen Petition. That postponement may well be sufficient to determine whether the FDA intends to dismiss the petition, as Plaintiffs will request, or address it on the merits. Moreover, two of the MDL's Co-Lead Counsel are also counsel in the Rodriguez case and will now need to divide their time between the looming trial deliverables deadlines and the need to properly respond to GSK's Citizen Petition, as is their obligation as members of the Plaintiffs' Steering Committee. Counsel for the Rodriguez Plaintiffs are available for a telephone conference with the Court this week to discuss an agreeable trial date or, if this Court wishes, submit a formal motion requesting the same.

II. ARGUMENT

A. GSK's Petition Represents a Misuse of the Citizen Petition Process

The Citizen Petition process exists in order to allow persons with no formal role before the FDA to request formal agency action, most often in the form of a request to the agency "to issue, amend, or revoke a regulation" or "to issue, amend, or revoke an order" of the FDA. 21 C.F.R. § 10.30(b)(3). GSK's petition does neither. It merely asks the FDA to "review four categories of information concerning the use of a prescription drug Zofran (ondansetron) in pregnancy," Petition at 1, and asks the agency to "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the Agency deems appropriate." *Id.* Further, and only if the FDA deems it appropriate to alter Zofran's pregnancy-related labeling in light of this information, the Petition asks FDA to "inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision." *Id.* GSK's Petition thus does not request that the FDA take any specific action concerning its regulations or orders, but merely asks the agency to

opine on the relevance of the four categories of information at the heart of the pending preemption motion.

The Citizen Petition regulation further requires the petitioner to supply the FDA with "representative information known to the petitioner which is *unfavorable* to the petitioner's position." 21 C.F.R. § 10.30(b)(3)(B) (emphasis added). Although GSK chose to provide FDA with *some* information relevant to each of the four categories of withheld information identified by Plaintiffs in response to the pending summary judgment motion, it chose selectively from this information and excluded much evidence supportive of Plaintiffs' claims.[1] This can easily be seen by comparing the Exhibits attached to the Citizen Petition with those provided by Plaintiffs in opposition to the pending motion. Moreover, GSK expressly requested that, in connection with this Petition, the FDA not consider more recent scientific developments that are directly relevant to Zofran's safety profile, including "newly available epidemiological studies and an assessment of Zofran's labeling by the Pharmacovigilance Risk Assessment Committee (PRAC)" of the European Medicines Agency, which support Plaintiffs' contention that Zofran's labeling should warn about and/or restrict Zofran's use during pregnancy. Petition at 1. In this respect as well, GSK's petition deviates from the proper use of the Citizen Petition process.[2]

[1] For example, GSK omitted the reports of Bengt Danielsson (a world-renowned teratologist) and Brian Harvey (a former FDA official who oversaw Zofran's labeling), as well the FDA's request for safety data related to NVP in 2010 and for "full details" of animal reproductive studies in 2014, and other internal documents reflecting GSK's concern about Zofran's teratogenicity dating back to 1995 and its hesitancy to study Zofran for fear of losing its Category B labeling status—among other relevant information.

[2] There is a separate FDA regulation, 21 C.F.R. § 10.85, that allows an "interested person" to request an "advisory opinion" from the agency through a process closely related to the Citizen Petition process. That regulation is nowhere referenced in GSK's petition. This is not surprising, even though GSK's Petition reads more like a request for an advisory opinion, because GSK's request is also inconsistent with the requirements of that section. In particular, 21 C.F.R. § 10.85 provides that a request for an advisory opinion must be on "a matter of general applicability," 21 C.F.R. § 10.85(a); the request may be denied if it "covers a particular product or ingredient or label

Because GSK's Citizen Petition is inconsistent with FDA regulatory requirements concerning that administrative process, Plaintiffs intend shortly to file a comment with the FDA urging the dismissal of the Petition.

B. GSK's Citizen Petition Represents an Improper Attempt to Interfere with This Court's Authority to Decide the Preemption Issue.

GSK offers no explanation to the FDA why it is seeking the FDA's views on the relevance and significance of "the four other categories of information" that GSK previously withheld from the agency. But it seems self-evident that GSK's purpose is to interpose the FDA's views on this question in an attempt to interfere with or even override this Court's authority to decide the pending summary judgment motion based on preemption. This GSK may not do.

As the FDA itself acknowledged in its amicus brief to the U.S. Supreme Court in *Merck v. Albrecht*, any determination concerning the legal effect of prior FDA actions on the viability of Plaintiffs' state-law claims is a question properly reserved for the Court itself to decide:

> "Where, as here, FDA renders a decision declining to approve a drug labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve…."
>
> "Just as the scope of a prior judicial adjudication is a question of law for a court to decide, so too is the scope of a federal agency adjudication like the one at issue here."
>
> "Where consideration of such material requires resolution of factual matters for a court to determine the meaning and scope of the agency decision, the court itself should resolve them."
>
> "To the extent extrinsic evidence may sometimes be relevant in litigation between private parties to determine the meaning and effect of FDA's agency action, the court's evaluation of such subsidiary facts does not alter the ultimate legal character of the inquiry or the court's *exclusive* authority to resolve it."

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and does not raise a policy issue of broad applicability." *Id. at* § 10.85(a)(2)(iv). Moreover, the request may be denied if it "contains incomplete information on which to base an informed advisory opinion." *Id. at* § 10.85(a)(2)(i). GSK's Citizen Petition falls short on both counts.

Brief for the United States as Amicus Curiae at 12–16, *Merck Sharp & Dohme Corp.*, 139 S. Ct. 1668, 1679 (2019) (No. 17-290), 2018 WL 4562163 at *15–21. The Supreme Court expressly concurred with this view in *Albrecht* when it ruled that only agency actions "carrying the force of law" can have preemptive effect under the "clear evidence" preemption rule; a hypothetical or potential conflict is insufficient to warrant … preemption." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1679 (2019) (quoting Rice v. Norman Williams Co., 458 U.S. 654, 659 (1982)); *see also id.* at 1682 (Thomas, J., concurring) ("Merck's primary argument, based on various agency communications, is that the FDA would have rejected a hypothetical labeling change submitted via the CBE process. But neither agency musings nor hypothetical future rejections constitute pre-emptive 'Laws' under the Supremacy Clause.") GSK clearly intends to ask this Court to view the FDA's 2019 (or 2020) opinion about what it would have done with Zofran labeling if GSK had years earlier submitted the withheld information as dispositive of the preemption question. But, as *Albrecht* teaches, neither "agency musings" nor "hypothetical or potential conflicts" are sufficient to justify preemption. Whatever the FDA may today say about what it hypothetically might have done if only GSK had submitted the withheld evidence concerning Zofran use during pregnancy at an earlier point in time cannot retroactively create the sort of "irreconcilable conflict" between state and federal law that would have given rise to "clear evidence" preemption. *Albrecht*, 139 S. Ct. at 1679 (quoting *Rice*, 458 U.S. at 659). The simple fact is that GSK did not submit this evidence to the FDA at the relevant time and thus any imagined conflict between FDA regulatory requirements and the requirements of the state-law duty to warn remain entirely "hypothetical."

C. GSK Must Disclose All of Its Communications With the FDA Concerning This Matter.

It seems clear, from numerous statements made by GSK to this Court, that GSK has been in frequent contact with the FDA about the possibility of submitting this Citizen Petition and/or requesting the FDA to submit an amicus brief to this Court on the pending preemption question. One might almost suggest that GSK seemed quite confident about the response it would receive from the agency even before it filed its Citizen Petition. Plaintiffs have a number of outstanding discovery requests to GSK that require the company to disclose *all* communications with the FDA concerning the use of Zofran during pregnancy.[3] To the extent that GSK has withheld information

[3] *See, e.g.*, Plaintiffs' Request for Production of Documents:

REQUEST NO. I.2: Produce all documents concerning communications between you and the FDA regarding Zofran's label.

REQUEST NO. I.7: Produce the documents and communications between you and any FDA employees concerning Zofran use during pregnancy, including internal documents that purport to discuss, reflect or summarize communications with FDA.

REQUEST NO. I.9: If you ever engaged any agent to communicate with the FDA concerning Zofran on your behalf produce: a. the documents and communications between the FDA and said agent(s) and b. the documents and communications between you and said agent(s).

REQUEST NO. II.6: Produce the documents and communications exchanged between GSK and the FDA or any other regulatory entity or official concerning Zofran animal studies that were conducted in Japan.

REQUEST NO. IV.14: Produce the documents and communications concerning any FDA request, inquiry, warning, or meeting, which pertain in any way to the safety, signal or signal detection, follow-up, or monitoring of patients exposed to Zofran.

REQUEST NO. VI.3: Produce the documents and communications concerning any discussions, negotiations, or contracts to engage any third-party to represent your interests before the FDA or any foreign governmental regulatory authority including any committee or subcommittee thereof regarding the possible side effects and/or the risk or occurrence of adverse events associated with the use of Zofran.

or documents concerning its more recent communications with the FDA, the Court should order GSK to disclose such information and documents as quickly as possible.

D. If the FDA Does Not Dismiss the Citizen Petition, Plaintiffs Must Be Permitted to Submit All Relevant Materials to the Agency, Including GSK-Produced Documents Currently Subject to Protective Order.

If the FDA declines to dismiss the Citizen Petition, Plaintiffs must be permitted to submit comments in order to supplement the record to provide the agency with a complete view of the information available to GSK and withheld from the FDA concerning the teratogenic risks posed by Zofran use during pregnancy. Many documents containing such information have been designated by GSK as "Confidential" pursuant to the protective order governing document production in this MDL. For the FDA review to have any credibility whatsoever, Plaintiffs must be permitted to provide the Agency with such "confidential" GSK documents. Unless the FDA promptly dismisses the Citizen Petition, Plaintiffs intend to come before this Court to request "de-designation" of GSK documents that may prove relevant to the FDA's review process.

E. No FDA Action on GSK's Citizen Petition Can Have Any Bearing on the Pending Motion.

There is no dispute between the Parties that GSK did not provide certain information to the FDA at the time of the agency's prior considerations of the appropriateness of a pregnancy warning for Zofran, including, most significantly, a number of the Japanese animal studies. Therefore, whatever FDA may today say in response to GSK's Citizen Petition can have no direct bearing on the preemption motion currently pending before the Court. As the Supreme Court explained in *Albrecht*, because the CBE regulation permits a drug manufacturer to add or strengthen a warning to a drug label based on new safety information not previously considered by the FDA, without prior approval from the agency, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both."

Albrecht, 139 S. Ct. at 1679. Plaintiffs have identified material safety information that GSK did not disclose to the FDA during its prior examinations of Zofran's pregnancy labeling. Thus, FDA never had the opportunity to consider the appropriateness of a pregnancy warning in light of that withheld information, and GSK remained free to use the CBE process to add a warning based on that undisclosed information. Whether the FDA would have denied permission to add such a warning at the time, based on that new information, remains an entirely "hypothetical" question; there is no "irreconcilable conflict" between state and federal law that would justify preemption.

A decision by the FDA on GSK's Citizen Petition will not alter that result. The FDA's speculation, in 2019, about what it might have done at an earlier point of time if it had been provided with that withheld information is just that—speculation. It cannot change the facts that FDA lacked that information at the time of its prior actions that GSK contends carry preemptive effect. Nor can FDA today decide whether Zofran should now carry a pregnancy warning without regard to the best and most recent scientific information available; yet that is precisely what GSK has asked the Agency to do. Newly available epidemiological studies (*Huybrechts* and *Zambelli*) report evidence of teratogenic effects of Zofran in human use during pregnancy, evidence which has led PRAC to recommend against ondansetron use during the first trimester of pregnancy. Any proper reevaluation of Zofran's labeling concerning use during pregnancy must take account of that new scientific and regulatory information, along with the scientific information GSK first disclosed to the FDA in its Citizen Petition. Absent such a comprehensive evaluation of the best current scientific information, any FDA statement in response to GSK's petition will constitute only the sort of "agency musings" that the Supreme Court explained in *Albrecht* lack preemptive effect.

III. CONCLUSION

GSK's Citizen Petition is a sideshow that should have no bearing on this Court's consideration of the pending renewed summary judgment motion. Although it seems clear that GSK filed the Petition in an attempt to interfere with the Court's consideration of that motion, and perhaps even with the intent to tell the Court that it must defer to FDA's decision on the Petition, *Albrecht* makes clear that GSK's petition is not the sort of formal agency action that would carry preemptive effect. This Court should not wait for, nor defer to, any FDA action in response to the Citizen Petition.[4] Instead, the Court should proceed to deny GSK's Motion for the reasons presented by Plaintiffs in their briefing and arguments. Nevertheless, Plaintiffs also request this Court delay trial until March 30, 2019, and also similarly extend the related pretrial deadlines by so that Counsel for the Rodriguez Plaintiffs may appropriately respond to GSK's Citizen Petition and seek relevant discovery.

Respectfully submitted,

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[4] If, however, the FDA proceeds with its consideration of the Petition over Plaintiffs' objections, the Court should authorize Plaintiffs to provide the FDA with full information concerning the issues raised, including the submission of GSK information currently designated as confidential pursuant to protective order.

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Dated: November 13, 2019

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CERTIFICATE OF SERVICE

I hereby certify that the foregoing Plaintiffs' Memorandum Concerning GSK's Citizen Petition and Request for Immediate Relief of the Rodriguez Trial Date and Pretrial Deadlines, which was filed with the Court through the CM/ECF system, will be sent electronically to all registered participants as identified on the Notice of Electronic Filing and paper copies will be sent via first class mail to those identified as non-registered participants.

/s/ *Kimberly D. Barone Baden*
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