**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF MASSACHUSETTS**

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

**GSK'S MEMORANDUM REGARDING ITS CITIZEN PETITION**

GSK submits this memorandum regarding its November 1, 2019 citizen petition in response to the Court's direction at the November 5 hearing.

GSK is confident that it is entitled to preemption based on the current record. Plaintiffs all but abandoned most of their arguments at the November 5 hearing. As this Court recognized after hearing the parties' oral arguments, Plaintiffs' argument against preemption "really boils down to Study 424." Ex. A (11/5/19 Hr'g Tr.) 65:21-25. The question before this Court is whether FDA would have viewed results from Study 100424 that cannot be distinguished from chance as material to its labeling decisions notwithstanding the conclusion of the study investigators that the study did not show teratogenicity and notwithstanding FDA's own conclusions that similar studies conducted both in the U.K. and Japan did not show teratogenicity. For all the reasons set forth at the hearing, that question cannot be resolved in Plaintiffs' favor without improperly second-guessing FDA's review of GSK's other animal studies.

To the extent this Court has any lingering doubt, FDA now has Study 100424 (and all the other information that Plaintiffs invoked in an attempt to defeat preemption). GSK has long been advocating for FDA's involvement, and in light of FDA's likely review of Zofran's labeling following developments in Europe, GSK invoked the only regulatory mechanism available to it to

request agency action: a citizen petition. It did so because it respects FDA's labeling decisions and authority and believes that Plaintiffs' arguments impermissibly subvert that authority.

FDA opened an official agency proceeding upon receipt of GSK's petition.[1] Federal law requires FDA to respond to the petition. Federal law also requires FDA to demand labeling changes if it "becomes aware of . . . new safety information" that it "determines should be included in the labeling of the drug." 21 U.S.C. § 355(o)(4)(A). If FDA believes that Study 100424 is material information that warrants a labeling change, it will act. FDA's response to the citizen petition thus will likely resolve the preemption issue. Although GSK is prepared to try the first bellwether case in January 2020, it would be appropriate and efficient for the Court to stay the trial date to allow FDA sufficient time to consider the citizen petition. It would also be appropriate for the Court to refer the matter to FDA or to send a letter to FDA to inform FDA of the relevance of the citizen petition to this MDL and to request a prompt response.

## I. The Citizen Petition Will Likely Dispose of the Preemption Issue.

FDA's resolution of GSK's citizen petition will likely resolve the preemption issue in this MDL. If FDA holds that Plaintiffs' four categories of information do not justify a labeling change and denies the citizen petition under 21 C.F.R. § 10.30, that agency action will establish preemption under *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). In that situation, even Plaintiffs could not dispute that FDA made its labeling decision while "fully informed" of all material information. *Id.* at 1678.

Plaintiffs suggested at the November 5 hearing that GSK's petition is an improper request for an "advisory opinion." Ex. A (11/5/19 Hr'g Tr.) 61:19-21, 69:17-21. Not so. As this Court acknowledged, and as Plaintiffs conceded, "denied action is a form of taking action." *Id.* at 71:12-

[1] GSK's citizen petition has been docketed at FDA-2019-P-5151.

14. The FDA's regulation governing citizen petitions expressly provides that a petition may request that FDA "refrain" from taking administrative action. 21 C.F.R. § 10.30(b)(3); *see also* 21 C.F.R. § 10.25(a) ("An interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."). If FDA "refrains" from requiring a labeling change after reviewing Plaintiffs' information, including Study 100424, and/or denies the petition, that is official agency action. *See* 21 C.F.R. § 10.30(e)(2)(ii) (providing that one agency response to a citizen petition is to "[d]eny the petition"). Notably, Plaintiffs have never disputed that FDA's denial of the Reichmann petition, and accompanying refusal to change the labeling, is agency action that has the force of law. GSK's petition is no different.

Plaintiffs also suggested that there is something improper about the fact that GSK did not analyze the recent epidemiological studies in its petition. Ex. A (11/5/19 Hr'g Tr.) 68:24-69:21. Analysis of those studies will presumably come from Novartis, the current NDA holder. GSK expressly noted the likelihood of that analysis in its petition; it was not hiding anything. It is precisely because FDA will likely be analyzing the labeling that GSK thought it appropriate to provide Study 100424 and Plaintiffs' other information to FDA at the same time. GSK is not asking for a "hypothetical" ruling "in the absence of all this other current science," as Plaintiffs incorrectly contend. *Id.* at 70:1-7, 71:5-11. GSK has asked for concrete FDA action to amend, or refrain from amending, the labeling under 21 C.F.R. § 10.30. Indeed, one possible outcome of the citizen petition is an FDA conclusion that a labeling change is required based on information, most notably recent epidemiological studies, that was not available at the time of the prior labeling decisions (or Plaintiffs' claimed injuries). If FDA requires a labeling change based only on newly available information, and not on Study 100424 or Plaintiffs' other information, preemption would

still be required in these cases since the alleged injuries at issue all occurred before such information was available. That action would confirm that FDA had all available material information at the time it made its prior labeling decisions.

At the November 5 hearing, Plaintiffs suggested that they need to know "why is [GSK] doing this." Ex. A (11/5/19 Hr'g Tr.) 62:18-22. As the Court seemingly recognized, however, a petitioner's motives for requesting agency action are irrelevant. *See id.* at 69:22-24 ("THE COURT: I mean, do the motives matter? In other words, I don't know what Reichmann's motives were. I don't know –"). It is agency action, not a petitioner's motives, that preempts state law under *Merck*. Here, in any event, GSK's motive is simple. GSK views Plaintiffs' argument against preemption as an attack on FDA's labeling decisions and authority. Plaintiffs' October 18 opposition to GSK's renewed motion crystallized their attack on FDA's labeling decisions: they affirmatively stated in their response to GSK's statement of undisputed material facts that FDA's conclusions about GSK's animal studies are "meaningless." Pls.' Resp. to GSK's Statement of Undisputed Material Facts ¶¶ 91, 128. They likewise spent much of their oral argument explaining why their expert believes that FDA's conclusions about the animal studies were wrong even though FDA determined that GSK had submitted the necessary animal reproductive toxicology studies to obtain approval for Zofran. *See* Ex. A (11/5/19 Hr'g Tr.) 39:14-41:23 (arguing, among other things, that "when these studies were done back in the late 1980's and early 1990's, dosing levels were far lower than they are today under modern ICH standards").

Unlike Plaintiffs, GSK welcomes FDA's views. GSK believes that FDA possessed all material information when it made its prior labeling decisions. For that reason, GSK did not initially submit Plaintiffs' categories of information to FDA when the preemption issue was first briefed. Nonetheless, ever since the Supreme Court decided *Albrecht*, GSK has been urging the

Court to refer the labeling issue to FDA under the doctrine of primary jurisdiction, to require Plaintiffs to file a citizen petition, or to request FDA to submit an amicus brief in this case. *See, e.g.*, ECF No. 1514, at 8-10 (June 3, 2019); ECF No. 1553, at 3-5 (July 1, 2019); ECF No. 1571, at 2-4 (July 9, 2019). Plaintiffs have resisted those efforts at every step, evidently fearful of what FDA would say. *See* Ex. A (11/5/19 Hr'g Tr.) 70:13-14 (MR. BOGRAD: "[P]laintiffs think that the Citizen's Petition should be dismissed rather than acted on."); Ex. B (7/10/19 Status Conf. Tr.) 26:25-27:1 (MR. MILROOD: "The FDA is not an outpost to resolve the latest updates on science."); *see also, e.g.*, Pls.' Supp. Mem. Addressing *Merck*, ECF No. 1549, at 15-18 (July 1, 2019); ECF No. 1572, at 7-10 (July 9, 2019). As recently as October 15, the Court suggested that it had not yet ruled out asking FDA for its views. *See* Ex. C (10/15/19 Status Conf. Tr.) 11:12-18.

Because GSK is not the NDA holder, its only mechanism for requesting FDA action itself is to file a citizen petition. When it became evident that FDA may soon review Zofran's labeling in light of recent epidemiological studies, GSK decided that it was an appropriate time to inform FDA of Plaintiffs' categories of information by filing a citizen petition. The petition is not an effort to delay this case; GSK is prepared to go to trial if necessary. The petition rather reflects GSK's firm conviction that federal law preempts Plaintiffs' claims and its desire to obtain FDA's confirmation to put this issue to rest.

GSK also believes that FDA's involvement is critical because FDA has repeatedly cautioned that issuing warnings that are not based in science could mislead the public and deter appropriate use of a drug. As this Court has recognized, "even today" pregnant women are being administrated Zofran. Ex. A (11/5/19 Hr'g Tr.) 56:11-17. FDA has long been aware of Zofran use in pregnancy, and it has cautioned that warning about birth defects "could be misleading." *See* Ex. D (FDA denial of Reichmann citizen petition) at 19. FDA also "recognize[s] that exaggeration

of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug . . . or decrease the usefulness and accessibility of important information by diluting or obscuring it." *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 659 (S.D.N.Y. 2017) (second alteration in original) (quoting 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008)), *aff'd sub nom. Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019). A jury verdict for Plaintiffs could well mislead physicians and the pregnant women who take Zofran to this very day. Given its expressed concern about that very result, FDA should weigh in regarding whether Plaintiffs' categories of information would have been material.

## II. It Would Be Appropriate to Stay the Trial to Allow the FDA to Decide the Citizen Petition.

GSK is prepared to go to trial on January 13, 2020 if this Court denies GSK's renewed motion for judgment based on preemption and denies GSK's general and specific causation *Daubert* motions and case-specific summary judgment motion in the *Rodriguez* case. (GSK believes that this Court can and should grant all of those motions on the current record.) Although GSK is prepared to try this case, GSK acknowledges that it would be an inefficient use of the parties', Court's, and jurors' time to try this case in January only to have the FDA later hold that Plaintiffs' information does not warrant a labeling change, requiring vacatur of any jury verdict in Plaintiffs' favor. *See* Fed. R. Civ. P. 52(b), 59, 60. Accordingly, it would be appropriate for the Court to stay the trial to conserve judicial resources.

If the Court decides to stay the trial, GSK submits that it would be appropriate to continue the trial date, at least through June 2020, subject to trial counsel's availability at that time. Under FDA regulations, FDA is required to furnish a response to GSK's citizen petition within 180 days of receipt. *See* 21 C.F.R. § 10.30(e)(2). Under that regulation, FDA's response would be due on April 29, 2020. However, the regulation authorizes FDA to "[p]rovide a tentative response,

indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information." 21 C.F.R. § 10.30(e)(2)(iv). "The tentative response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished." *Id.* At this point in time, GSK cannot predict whether FDA will provide a final response on April 29, 2020, or, if not, when it will provide a final response. That said, if the results of Study 100424 were truly material, one would expect FDA to act quickly to inform doctors.

Continuing the trial date at least through June 2020 would give the parties time to brief the implications of FDA's response to the citizen petition and would give this Court time to rule on preemption in light of FDA's response. It would also give the parties and Court time to consider whether the trial should further be postponed in the event that FDA is unable to reach a decision by April 29, 2020.[2]

**III. The Court May Wish to Refer the Matter or Send a Letter to FDA.**

Now that FDA will be deciding GSK's citizen petition, it would be particularly appropriate for the Court to invoke the referral mechanism in 21 C.F.R. § 10.25(c) and refer this matter to the FDA "as a means of coordinating administrative and judicial machinery." *Pejepscot Indus. Park, Inc. v. Maine Cent. R. Co.*, 215 F.3d 195, 205 (1st Cir. 2000) (quoting *Mashpee Tribe v. New Seabury Corp.*, 592 F.2d 575, 580 (1st Cir. 1979)); *see* ECF No. 1514, at 8-10 (discussing the doctrine of primary jurisdiction). To be clear, the Court need not invoke § 10.25(c) to "take advantage of [FDA's] special expertise." *Pejepscot Indus. Park*, 215 F.3d at 205. GSK has already invoked the regulatory process by filing a citizen petition, and the Court need only wait for FDA's response. *See Palmer Foundry, Inc. v. Delta-HA, Inc.*, 319 F. Supp. 2d 110, 113 (D. Mass. 2004)

[2] Plaintiffs' proposal to postpone trial until March 30, 2020, should be rejected as it would not provide sufficient time for the Court to receive a response from FDA on the citizen petition.

(explaining that when courts invoke the doctrine of primary jurisdiction, they typically stay proceedings "to allow one of the parties to file an administrative complaint seeking resolution of a particular issue"). But, if the Court were to refer the matter to FDA under § 10.25(c), that action may well incentivize FDA to decide the petition more promptly than it otherwise would.

At a minimum, the Court may wish to send a letter to FDA's Chief Counsel's Office advising of the relevance of the citizen petition to preemption and encouraging FDA to provide its views in an amicus brief. Such a letter, which would carry the imprimatur of a co-equal branch of government, may similarly incentivize FDA to decide the petition promptly. GSK proposes the following language for such a letter:

> The Court is presiding over an MDL proceeding in which plaintiffs allege that Zofran causes birth defects. On November 1, 2019, GlaxoSmithKline (GSK), the former NDA holder, submitted a citizen petition requesting "that FDA 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." The Court is currently assessing GSK's renewed motion for summary judgment based upon federal preemption. GSK's citizen petition raises issues relevant to that motion. The Court encourages FDA to resolve the citizen petition as promptly as possible. Additionally, if FDA wishes to submit an amicus brief setting outs its position on any aspect of the preemption issue before the Court, the Court requests that FDA do so on or before [date].

## CONCLUSION

For these reasons, it would be efficient for the Court to stay the trial while FDA decides GSK's citizen petition, which will likely resolve the preemption issue in this case.

Dated: November 13, 2019

Respectfully submitted,
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**CERTIFICATE OF SERVICE**

I hereby certify that the foregoing document, 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 ("NEF") and paper copies will be sent via first class mail to those identified as non-registered participants.

*/s/ Jennifer Stonecipher Hill*
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# EXHIBIT A

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (Ondansetron) PRODUCTS LIABILITY LITIGATION ) MDL No. 15-02657-FDS

BEFORE: THE HONORABLE F. DENNIS SAYLOR, IV

MOTION HEARING
FOR SUMMARY JUDGMENT BASED ON FEDERAL PREEMPTION

John Joseph Moakley United States Courthouse
Courtroom No. 2
1 Courthouse Way
Boston, MA 02210

November 5, 2019
9:00 a.m.

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And GSK wrote back and said, Ah, here are the four studies we've given you previously and continued to ignore the Japanese animal studies.

Again, when FDA turned down *Novartis*' request to add a pregnancy warning, they said in part that they were doing so because there was no evidence of reproductive -- teratogenic reproductive effects in the animal studies, so, again, clearly the FDA has said loud and clear we care about evidence of nonclinical studies that reveal birth defects.

09:57AM And that makes perfect sense, of course, your Honor, because, as we know, we don't test drugs on pregnant women, so tests on pregnant animals are the best evidence we have of the implications of a various drug product for human reproduction.

Now, so that's it. So I don't think we even need to get to the discussion of the expert testimony, but if we do, Dr. Danielsson provides elaborate analysis of why the Japanese animal studies mattered and explains why this obsession with the background rate of -- the background rate of birth defects in the general population is the wrong way to look at the

09:58AM question, and Dr. Danielsson's not making this stuff up himself, he's invoking the ICH protocols for analyzing reproductive toxicology, and the ICH protocols say that you need to do a comprehensive assessment, that, you know, you need to take into account biological mechanism of action, you need to look at dose relationship, you need to look at

reproducibility across species, all the sorts of things that are exactly the steps he takes and that GSK's experts have not.

It is significant to note, your Honor, that GSK did not have studies on the fetal dose exposure at the time that they were conducting the U.K. and I think as well the Japanese animal studies.

They had no idea, given the rapid half life with which Zofran is absorbed by rats and rabbits. They had little to no information about how much Zofran was getting to the embryonic animals, which is critical in assessing reproductive toxicity and teratogenicity.

And as Dr. Danielsson explains at some length, based upon the information we have about the way in which Zofran crosses the placental barrier and based on the information how quickly it can dissipate, we can estimate, you know, what dosing -- it's not as simple as, well, milligrams per kilogram, rats are smaller than humans, therefore, a smaller dose is equivalent.

We have to estimate, make calculations about what amount of Ondansetron is likely to actually get through to the embryo at the critical points in time in order to make an assessment, and Dr. Danielsson concluded that the only cases in both the U.K. and Japan studies in which dosing levels were high enough to -- and I've got a slide here, which I can refer

to in a minute with a citation from his deposition -- that it was only in a few most high dose -- sorry, that when these studies were done back in the late 1980's and early 1990's, dosing levels were far lower than they are today under modern ICH standards, and that there are only a limited number of studies, of occasions in these studies at the very highest doses where the amount of -- where the Zofran dosing was sufficient to reproduce the level of embryonic exposure that we would expect in a human embryo, and it is in precisely those instances where we see cardiac defects in the treated rats. And it is a dose response. It's only where these doses are high enough that we see any response whatsoever.

10:01AM

In addition, the ICH guidelines say that when you compare these -- that when you look at details, you need to be comparing the properly dosed animals to the controls of the same species, not to some presumed background rate in the general population because these are very carefully bred animals with unique characteristics.

The question is not the background rate among rats in general but are we seeing incidence of cardiac malformations in these highly dosed animals as compared to the controls of the same species in the same test, and, indeed, the Japanese animal studies find exactly that.

10:02AM

Now, as I said at the beginning, I don't think the question is whether the FDA would have changed its mind if it

Now, I don't know if FDA may have that independently in some way. I know the PRAC people do.

It's published, yeah, so I think they would have it because that's published literature, and it's possible that Novartis sent that to them, but that was never one of the categories in the preemption record.

THE COURT: What about the timing of this? And I'll say one of the things that I have struggled with for a long time in this litigation is -- and really this falls on both sides.

If plaintiffs are right and pregnant women are being administered this drug without proper warnings, even today, and it's resulting in children being born with septal or orofacial defects, why haven't plaintiffs' counsel or plaintiffs' physician experts run to the FDA and said, Stop, stop, stop, there's this nightmare of birth defects unfolding, even as we speak, you need to take action?

On the other hand, defendants have been saying for four years that this is all a bunch of nonsense, and you could have gone to the FDA and said, you know, here's all this information, you decide this issue.

But here we are really pretty close to the eve of the first Bellwether trial, and now we have a Citizen's Petition, and the timing of it is -- well, I expect we're going to hear from plaintiffs that the timing of it is troublesome, but

decided to take an end-run and take it into their own hands without notifying the plaintiffs, without notifying this Court, without telling us, or supplementing their discovery what it knew and when it knew it.

There have been regulatory requests for production and interrogatories that have been standing in this case for a long time, including their interaction with Novartis and communications to the FDA. GSK had an obligation under the rules of discovery to let us know about that.

10:42AM THE COURT: I'm sorry, what has been withheld do you think or not produced as discovery?

MR. MILLROOD: You know, we've noticed that in the last few pleadings, and including in Ms. McDonough's statements this morning, that they're aware of something, "We know that the FDA is about to do something." How do they know that?

What is it that they know that's happening from a regulatory perspective that they're not letting the plaintiffs know?

And what was remarkable about this filing with the 10:43AM FDA, this was an advisory opinion sought for litigation purposes. The whole thing was about litigation. This wasn't about -- it's talking about plaintiffs and plaintiffs' theories and 400 cases are pending, and here's what Dr. Danielsson's expert report says in the case, and they're looking for an assist from the FDA in this litigation.

Now, we have no idea what Novartis has provided to the FDA, what requests came to Novartis. I will tell you that Novartis is represented by Martin Calhoun of Collingsworth, and when Ms. McDonough said earlier this summer, hey, there's something going on in Europe, I don't know whether it will be relevant here, but there's some discussion with the agency over there, and we may bring it to your attention.

Immediately after that, I picked up the phone and I called Novartis' counsel, and I said, "Would you like a subpoena or will you cooperate with me to provide to me whatever you're providing to the regulatory agency over there?" He got back with me and said, "No problem, you don't need to send me a subpoena, I'll provide that information to you."

I've never gotten it. I've never gotten the information into the Europe agency, and I've certainly gotten no discovery provided to me by GSK as to what's happening with the FDA.

So here's what we think is the procedural impact of this. We have to take discovery. We have to find out what did GSK know and when did it know it, and why is it doing this, and what are the regulatory communications, what is Novartis communicating?

There was a representation -- you asked counsel for GSK, Did you give them everything? Well, I can represent to this Court, having reviewed the Citizen's Petition, they've not

given everything that's relevant.

The Citizen's Petition regulations require that you not only produce what you want to the FDA, but you have to produce a contrary position for the FDA to consider. They did not produce contrary positions deliberately because they're looking for this assist of an advisory position in the litigation, so, presumably, there will be some kind of comment period. We will have to provide the FDA what GSK chose not to provide, which was the contrary position and contrary evidence.

10:45AM And with that, GSK also told this Court a couple of months ago that they were going to be perhaps involving the FDA, if this Court permits that, and to do that, they were going to have to de-designate a whole bunch of documents. You may recall GSK counsel told you that.

Now, we have refrained for five years, your Honor, from coming to this Court seeking the de-designation of documents. We believe that the arena here, although many of these documents should not have the protection of confidentiality, we've stayed within the arena of this

10:46AM litigation here, but if the FDA is going to consider this and consider this for litigation purposes, we're going to have to provide them with documents, and we're going to have to also seek this Court's permission for the de-designation of documents.

This question that's been raised about why is it that

plaintiffs aren't running to the FDA for some kind of support or Citizen's Petition, you know, it's interesting that in the context of preemption, it's long been recognized that the reason why we're permitted, and *Wyeth vs. Levine* underscores this, the reason why we're permitted to bring these lawsuits here is because there's a parallel system that exists.

The FDA exerts its regulatory authority over the manufacturer, and plaintiffs are permitted to seek a state court tort system or state tort law to seek redress for their injuries.

Our clients have hired us to come into these courts and seek redress for their injuries. I can tell you that in my own agreements with my clients in terms of what I tell them is the scope of my representation with them, I don't tell them I'm representing you before the FDA to try to seek a change in the label.

Now, it may be interesting strategy, it may be helpful to it, but what we're duty-bound to do is to seek for redress for our clients under the tort system.

10:47AM THE COURT: No, I understand, but this is -- you know, the paradigm of the pharmaceutical case is products on the market, it turns out people discover, let's take DES, you know, a classic example.

People discover, the scientists discover, you know, it can cause cancer in offspring exposed in utero, and the product

is either pulled off the market or it's contraindicated for pregnancy, or whatever, and now you have litigation.

What studies, what tests were done, it's all under the heading of failure to warn, you didn't do proper testing, and, therefore, you didn't warn the pregnant women, but the decision has been made or the scientific consensus is clear down the road that this is a problem, that DES can cause, whatever it is, carcinoma of the cervix or the vagina or whatever it is that the problem is.

10:48AM And this is kind of different because the product is still on the market and still isn't bearing any warnings, and so we're in this peculiar posture, at least from my standpoint, that even today, this morning some pregnant woman woke up and took this pill, and maybe you haven't struggled, but I've struggled with that.

What does that mean in this context? What are we -- you know, if you're right, and maybe you are, but if you're right, shouldn't those women be warned? Shouldn't their physicians be warned? Shouldn't they know about the dangers of

10:49AM this product?

So we have that, and the preemption argument really boils down to -- I mean, I know it's not quite as simple as this, but it really boils down to Study 424. I mean, that's the meat of this dispute is should that have been disclosed to the FDA back in 1991 or whenever it was?

Now, the FDA has the study, so what do I do with that? At least, I think they have it. And if they look at it and say, yeah, well, we don't care, where does that leave this litigation?

And if they say, Ho-ho, this is a game changer, this should be Category C or the modern equivalent of Category C, whatever that is, now, you know, you're in a much stronger position, so, you know, I'm thinking out loud here. I've had 24 hours, at most, to think about this issue, but...

10:50AM MR. MILLROOD: Your Honor --

THE COURT: I'm sorry, go ahead.

MR. MILLROOD: -- I will say that as counsel for GSK noted, they're not the label holder, and so far as we could tell from the reading of the Citizen's Petition, it was a little bit vague, but I did not read it to say they are requesting a specific labeling action.

THE COURT: Well, they're not the manufacturer anymore, right?

MR. MILLROOD: Correct.

10:51AM THE COURT: So I think they say take action or not.

MR. MILLROOD: Exactly. We would ask that you refrain until we kind of know which of these four categories are meaningful to you and how, if at all, they would go into the label, so, again, they're asking the FDA for some kind of advisory opinion.

Now, even if -- and, again, I don't know if there's a Novartis request, I don't know if there's a labeling change requested by Novartis or something requested of Novartis. GSK apparently seems to know that. We don't know that, but even if the FDA acted on this current Citizen's Petition, I'm not sure that it would affect the answer to what we're looking at in this litigation. It may further inform us, but it's not official agency determination as to the label in this case.

THE COURT: Well, I mean, that's one of the questions, isn't it? I mean, there's three possibilities. The agency could take no action, just said, thank you, we've considered it, we're not changing the label.

Is that an agency decision? I forget, Justice Alito mentions it in his concurrence, but, you know, it seems to me they've done something. Maybe that means something; maybe not. They could say no, the label stays in place. They could say, Ah-hah, we need to change the label, we have been deceived, or the third possibility, they could do something in between there.

10:52AM It seems to me if they go with Option Number 1, let's say the Rodriguez case goes to trial. Let's say you win $100 million, then on May 1st, FDA says, no, we think the label should have stayed where it was, even taking into account the Japanese animal studies and Dr. Danielsson and everything, then what do I do then? Don't I need to vacate that verdict and

think about it from scratch?

MR. BOGRAD: Your Honor, can I respond?

THE COURT: Yes. I know without the benefit of briefing, which I may order when I'm done with all this, but I'm thinking out loud, okay, and this is what's on my mind.

MR. BOGRAD: That's what we're all doing, your Honor.

THE COURT: Yes.

MR. BOGRAD: A couple of reactions. First, apart from this litigation, it's our view that this is a misuse of the Citizen Petition process to begin with. The Citizen's Petition process exists so that anyone can go to the FDA and request formal regulatory action, whether it's a new regulation, whether it's a change in a label. You go to the agency, you say here's all this information that leads me to believe that you should regulate smokeless vaping cigarettes.

10:53AM

THE COURT: Right.

MR. BOGRAD: Here's this information that leads me to believe that we should add a pregnancy warning to this drug. That's what a Citizen's Petition is supposed to be for for a formal regulatory action based upon the best available science, including science that both supports, and, as Mr. Millrood said, contradicts the position of the petitioner. That's not what this is.

10:54AM

As GSK notes in the very first paragraph of its petition, there's all this stuff going on about Zofran, you

know, over in Europe with the Pharmacovigilance Risk Assessment Committee and of the European Medicine's Agency and ENTIS, which is the European Network of Teratology Information Services, who take a different interpretation of what PRAC recommended, though they likewise recommend that Zofran should at best be second line therapy for use during pregnancy. There are these new epidemiologic studies that underlie the PRAC recommendations.

GSK says ignore all that, you know, or deal with that with Novartis, that's not what we're asking about.

We are asking you a hypothetical question. If we ignore all that information but only look at these pieces of information that the plaintiffs have pointed to that they dug out of our files, you know, would that be sufficient to lead you to change the label? Is that information that you had or deduced, or, you know, did you go on Toxnet to look it up?

You know, they're asking for an advisory opinion for the equivalent of an amicus brief in this litigation, they're not asking for formal agency action. We think as a matter of FDA regulatory procedure, that's an inappropriate use of the Citizen Petition process.

THE COURT: I mean, do the motives matter? In other words, I don't know what Reichmann's motives were. I don't know --

MR. BOGRAD: It's not that motives matter, it's that

I'm saying that relief that is requested seems very odd. They are specifically saying to the agency, we want you to answer these questions in the absence of all this other current science, you know, that we don't want you to ask should there be a pregnancy warning in light of this information and these new human epidemiologic studies. That would be a perfectly appropriate Citizen Petition.

They are saying, no, no, Novartis can deal with you about that stuff, we want you to tell us whether we should be entitled to preemption because we didn't give you these studies 20 years ago, and we think that's an abuse of the process, but we also think, and for that reason, while we have certainly made no decisions yet, I think plaintiffs think that the Citizen's Petition should be dismissed rather than acted on.

If it were to be acted on, I think the record needs to be substantially supplemented from what GSK provided.

THE COURT: Is there a mechanism for dismissing a Citizen's Petition? Can you oppose it?

MR. BOGRAD: One of the options they have is to dismiss. What we have to figure out is what our options are to participate and whether, if we move to dismiss, we somehow preclude ourselves from submitting additional information.

But as far as this case goes, your Honor, I also think the Citizen's Petition does not answer the preemption question precisely because they have not asked the agency to decide,

given the best science today, whether there should be a pregnancy warning, they have asked the agency what would you have done back in 1991, or whatever year it was, if we had given you this information?

That's precisely the kind of hypothetical preemption that the Supreme Court explicitly says doesn't count under *Merck v. Albrecht*, that that's, you know, that the only -- impossibility doesn't kick in unless and until the agency was given an actual, you know, was presented with an actual regulatory situation and took action, and if that implicated --

10:58AM

THE COURT: Or not took action.

MR. BOGRAD: Or not, yes, right, denied action is a form of taking action. Yes, I certainly agree, but that, you know, asking the question what would the agency have done had it had this information, which is the question the Citizen's Petition asks is not the question for clear evidence preemption under *Merck v. Albrecht*, I mean, you know, as the possibility of impossibility is not enough, hypothetical or potential conflict is not sufficient to preempt state law. That's what the Court says, and it says it repeatedly.

10:58AM

Now, you had asked a question, I wasn't at the hearing, I think it was in July, where we were discussing the timing issues about these things.

The question I think you were asking, just asking us

# EXHIBIT B

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (Ondansetron) PRODUCTS LIABILITY LITIGATION ) MDL No. 15-02657-FDS

BEFORE: THE HONORABLE F. DENNIS SAYLOR, IV

STATUS CONFERENCE

John Joseph Moakley United States Courthouse
Courtroom No. 2
1 Courthouse Way
Boston, MA 02210

JULY 10, 2019
1:30 p.m.

Valerie A. O'Hara, FCRR, RPR
Official Court Reporter
John Joseph Moakley United States Courthouse
1 Courthouse Way, Room 3204
Boston, MA 02210
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and the Supreme Court in *Merck* said that is not an official agency decision that would allow a defendant to be immuned under preemption.

THE COURT: Even if subsequent science or subsequent agency decisions said that that was wrong or it didn't make a difference?

MR. MILLROOD: That's right, your Honor, and I would submit that under the hypothetical that you raised last time in our June status conference, if there was some study out there of a million women that showed no risk, maybe Zofran's protective of birth defects, the vehicle at that point in time would not be an FDA decision or preemption, it would be a motion for summary judgment on general causation.

The question as it relates to preemption is an official agency decision at the time the warning is considered or should have been considered through a CBE or what not, but the fact that there's going to be -- your Honor, again, under that view, we could be in the middle of trial, and the *Journal of Reproductive Toxicology* could out with a new study that GSK views it one way that says, oh, Zofran is really safe, and we'd be pausing the trial to say, well, let's send this down to the FDA to see what they think.

That is not what *Merck* says is the way to set this thing up. That's not how you resolve the question of preemption. The FDA is not an outpost to resolve the latest

updates on science.

THE COURT: Okay.

MR. MILLROOD: Thank you, your Honor.

MS. McDONOUGH: Well, there were a lot of hypotheticals I think in Mr. Millrood's argument and maybe some leaps of logic, so I guess what I wanted to start with is your question, which I think was very appropriate. We now have the *Albrecht* decision.

What it said for the first time making it really clear is preemption is an issue for the Trial Judge, not for the jury. We didn't know that for sure at the time that you made previous rulings.

We said we thought it was a legal question, but that was not really set forth yet by the Supreme Court. Now they've done that. You asked the appropriate question, okay, what do I do now because I didn't make factual findings before, I was planning to give that to the jury, I did not reject preemption, I was planning to give that to the jury, so those things were not decided before, but now *Albrecht* has said, you know, it's an unenviable task, but the Trial Judge has to now sort out the preemption questions.

What did the FDA know, whether it was provided to FDA by GSK or someone else, a Citizen's Petition, publicly-available information, whatever, did the FDA know of the issue and the science and the relevant facts when it made

# EXHIBIT C

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (Ondansetron) PRODUCTS LIABILITY LITIGATION ) MDL No. 15-02657-FDS

BEFORE: THE HONORABLE F. DENNIS SAYLOR, IV

STATUS CONFERENCE

John Joseph Moakley United States Courthouse
Courtroom No. 2
1 Courthouse Way
Boston, MA 02210

October 15, 2019
11:00 a.m.

Valerie A. O'Hara, FCRR, RPR
Official Court Reporter
John Joseph Moakley United States Courthouse
1 Courthouse Way, Room 3204
Boston, MA 02210
E-mail: vaohara@gmail.com

right now, but, let's see, this Friday is the 18th. How about 10 days? I don't want to ruin your weekend, Ms. Hill.

MS. McDONOUGH: They're begging for 12.

THE COURT: How about 11? October 29th.

MS. McDONOUGH: We'll do what you suggest, your Honor.

THE COURT: I don't think this is in the calendar for an argument, right?

MS. McDONOUGH: No, that was the next question. You know, the sooner, the better, given the trial schedule, and all
11:09AM the other things going on.

THE COURT: Yes.

MS. McDONOUGH: While we're talking about that, I mean, it would be good to know if you are still considering asking the FDA for any guidance or an amicus brief, if you want a bench trial on this topic, any of those other outstanding questions we would like to have guidance on.

THE COURT: A somewhat simplified answer is I want to read your briefs.

MS. McDONOUGH: Okay. Thank you.

11:10AM MR. MILLROOD: Your Honor, briefly on this, so we will be timely filing our opposition this Friday. Last Friday, GSK wrote us an e-mail to indicate that they planned to file a motion to amend the statement of facts in its brief and wanted to know without seeing what that would look like whether we would object.

# EXHIBIT D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

OCT 2 7 2015

James P. Reichmann
[redacted]

Re: Docket No. FDA-2013-P-0048

Dear Mr. Reichmann:

This letter responds to your citizen petition received on January 7, 2013,[1] and the supplemental information submitted by you and received on January 14, 2013, March 12, 2013, May 14, 2014, June 24, 2015, and September 14, 2015 (collectively, the Petition).[2]

The Petition states that the use of Zofran (ondansetron) by pregnant women poses risks to the fetus, neonate, and mother and that there is insufficient evidence to support the unapproved use of ondansetron for the treatment of nausea and vomiting during pregnancy.

The Petition requests that the Food and Drug Administration (FDA or Agency) take the following actions (Petition at 2):

- Reclassify the drug ondansetron (Zofran) from pregnancy risk category B to category C, D, or X after evaluation of "new safety information";
- Notify obstetricians and gynecologists (OB/GYNs) that there is insufficient scientifically acceptable evidence that ondansetron is associated with improved treatment outcomes and may lead to adverse maternal and fetal events or outcomes;
- Notify OB/GYNs that promotion of continuous subcutaneous ondansetron pump for the treatment of nausea and vomiting of pregnancy (NVP) is a violation of FDA regulations.

[1] Although this citizen petition was received on January 7, 2013, it was dated January 4, 2012. We believe that the year of 2012 on the Petition was a typographical error. Also, because the Petition is not page-numbered and includes a cover page, for purposes of this response we consider the cover page to be part of the Petition, and refer to the Petition page numbers accordingly (i.e., the cover page is considered page 1 of the Petition).

[2] Anonymous submissions in support of the Petition were received on September 3, September 24, and October 29, 2013, and on January 23, April 14, and September 26, 2014. A signed submission opposing the Petition was received on January 27, 2014. Signed submissions in support of the Petition were received on February 2, February 9, March 6, April 20, April 27, and October 5, 2015.

We have carefully considered the Petition and submissions to the docket. The Petition's requests are denied for the reasons described below.

## I. BACKGROUND

### A. Ondansetron Indications and Unapproved Use

#### *1. Approved Indications*

Ondansetron is a type three 5-hydroxytryptamine receptor antagonist indicated for use in the prevention of nausea and vomiting associated with chemotherapy and radiotherapy and the prevention of postoperative nausea and vomiting associated with anesthesia.

FDA-approved and currently marketed ondansetron drug products[3] include the formulations in Table 1, below. Ondansetron is marketed under the trade name Zofran (all dosage forms except oral film) or Zuplenz (oral film only).

Table 1—Currently Marketed Approved Ondansetron Drug Products

| Approval Year | Dosage Form | New Drug Application (NDA) No. | NDA Holder |
|---|---|---|---|
| 1991 | Injectable; Injection | 20007 | Novartis |
| 1992 | Oral tablet | 20103 | Novartis |
| 1997 | Oral solution | 20605 | Novartis |
| 1999 | Orally disintegrating tablet | 20781 | Novartis |
| 2010 | Oral film | 22524 | Galena BioPharma |

In addition, generic versions of the NDA products are available in all dosage forms, except for oral film.

The approved indications of ondansetron for injectable products are:

1. Prevention of nausea and vomiting in patients aged 6 months and older associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.
2. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients in whom nausea and/or vomiting must be avoided postoperatively, [Product Name(s) and Formulation(s) is/are] recommended

[3] For the injectable, oral tablet, and oral solution dosage forms, ondansetron hydrochloride is used. For the oral disintegrating tablet and oral film, ondansetron base is used. For purposes of this response, all forms will be referred to as ondansetron.

even when the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic [Product Name(s) and Formulation(s) is/are] and experience nausea and/or vomiting postoperatively, [Product Name(s) and Formulation(s) is/are] may be given to prevent further episodes. [Product Name(s) and Formulation(s) is/are] approved for patients aged 1 month and older.

The approved indications of ondansetron for oral products (oral tablets, orally disintegrating tablets, oral solution, and oral film) are:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 milligrams (mg)/meter $(m)^2$.
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
4. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, [Product Name(s) and Formulation(s) is/are] recommended even where the incidence of postoperative nausea and/or vomiting is low.

2. *Unapproved Use*

No ondansetron drug product has been approved for the treatment of nausea and vomiting in pregnancy (NVP).

We are aware of the unapproved use of oral and injectable ondansetron for the treatment of NVP. NVP is a common condition affecting 50% - 90% of women during their pregnancies.[4] The severity of NVP exists on a continuum, and the most severe form is known as hyperemesis gravidarum (HG). HG has been reported in 0.5% to 2% of pregnancies and is characterized by persistent and severe nausea and vomiting that may be accompanied by weight loss, large ketonuria, electrolyte abnormalities, and dehydration. HG can pose a risk to the health of both the mother and the fetus and may result in hospitalization. Between 2004 and 2008, approximately 3% of a sample of 4,300 expectant mothers enrolled in the Slone Epidemiology Center Birth Defects Study reported using ondansetron in the first trimester of pregnancy.[5]

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[4] Piwko C, et al., "Economic burden of nausea and vomiting of pregnancy in the USA." *J. of Population Therapeutics & Clin Pharm* 2013; e149.

[5] Mitchell AA, Gilboa SM, Werler MM, et al. "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008." *Am J Obstet Gynecol* 2011;205:51.e1-8.

## B. Pregnancy Risk Labeling for Ondansetron

### *1. Pregnancy Risk Categories in Prescription Drug Labeling*

At the time the Petition was submitted in 2013, FDA regulations required the *Pregnancy* subsection of the drug product labeling to address the teratogenic effects of the drug by inclusion of the appropriate pregnancy risk category, as well as the relevant required statements for that category unless a drug was not absorbed systemically and the drug was not known to have a potential for indirect harm to the fetus (21 CFR 201.57(c)(9)(i) and 201.80(f)(6)(i)).

### *2. Current Ondansetron Labeling Regarding Use during Pregnancy*

During the NDA review and approval process for Zofran (the first approved ondansetron drug product), FDA determined that pregnancy risk category B was the appropriate category. Other ondansetron drug product applications (for both NDA and generic products) have likewise been assigned pregnancy category B. The regulations in effect when the Petition was submitted in 2013 specified the following criteria for a pregnancy risk Category B designation:

- "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women" or "animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(2) and 201.80(f)(6)(i)(b)).

The current approved labeling for injectable ondansetron products states the following in the Pregnancy section:

> **Pregnancy; Pregnancy Category B**
>
> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The current labeling for oral ondansetron products other than oral film (oral tablets, orally disintegrating tablets, and oral solution), states the following in the Pregnancy section:

> **Pregnancy: Teratogenic Effects**
>
> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The current labeling for the oral film formulation of ondansetron states the following in the Pregnancy section:

> **Pregnancy**
>
> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively (approximately 8 and 30 times the human dose of 16 mg/day, based on body surface area), and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, [Product Name] (ondansetron) oral soluble film should be used during pregnancy only if clearly needed.

However, as discussed below, the requirements for prescription drug product labeling with regard to potential risks during pregnancy and lactation recently changed.

*3. Pregnancy and Lactation Labeling Rule (effective June 30, 2015)*

On December 4, 2014, FDA issued a final rule amending the regulations concerning the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule).[6] The changes to the regulations took effect on June 30, 2015. The Pregnancy and Lactation Labeling Rule requires the following:

- Labeling for drug products that are the subject of applications (including NDAs, Biologics License Applications (BLAs), and efficacy supplements) approved on or after June 30, 2001, must comply with the content and format requirements in 21 CFR 201.57(c)(9)(i), as revised by the Pregnancy and Lactation Labeling Rule.[7]

[6] *Federal Register* (FR) notice, "Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," (79 FR 72064, December 4, 2014).

[7] See 21 CFR 201.56(b); 21 CFR 201.57(c)(9)(i).

- For all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, the pregnancy letter categories A, B, C, D, and X must be removed.[8]

A holder of an application that is not subject to the new content and format requirements of the final rule (i.e. an application subject to 21 CFR 201.80) must remove the pregnancy risk category from its labeling within 3 years after the effective date of the rule.[9] A holder of an application that is subject to the new content and format requirements of the rule (i.e., an application subject to 21 CFR 201.56) is required to remove the pregnancy category when it revises the labeling of the product according to the implementation schedule in the Pregnancy and Lactation Labeling Rule.[10] Because of this phased implementation schedule, there may be a window of time during which the pregnancy risk categories continue to appear on some ondansetron drug product labeling, while other ondansetron products have labeling that has been revised consistent with the Pregnancy and Lactation Labeling Rule content and format requirements.

## II. DISCUSSION

The Petition states concerns regarding certain potential risks to the fetus and neonate (e.g., cleft palate) and to the pregnant woman (e.g., Torsade de Points and QT prolongation) if she receives ondansetron during pregnancy (Petition at 3-4), particularly during unapproved use of ondansetron to treat NVP. These potential risks are discussed in section II.A (Discussion of Risks) below.

The Petition also requests that FDA take specific actions with regard to such potential risks, including: (i) changing the pregnancy category of ondansetron; (ii) providing certain notifications to OB/GYNs regarding the safety and efficacy of ondansetron use during pregnancy; and (iii) providing certain notifications to OB/GYNs regarding marketing or promotion of a continuous subcutaneous pump to deliver ondansetron for the treatment of NVP. These requests are discussed in section II.B (Petition Requests) below.

### A. Discussion of Risks

#### *1. Risks to the Fetus and Neonate*

The Petition raises a safety concern regarding teratogenic and other risks to the fetus and neonate in support of the request that FDA reclassify ondansetron from pregnancy category B to category C, D, or X, based on new safety information. In particular, the Petition alleges that the use of ondansetron during pregnancy may result in an increased risk of cleft palate or other fetal and neonatal anomalies. The Petition includes citations

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[8] 21 CFR 201.57(c)(9); 21 CFR 201.80; see also 79 FR 72064 at 72095.

[9] See 79 FR 72064 at 72095.

[10] Id.

to a number of studies and case reports. We discuss these points below. We then describe additional clinical and other information we reviewed, discuss our analysis of this information, and provide our conclusions. For the reasons discussed below, we deny the requests.

*a. Studies Cited in the Petition (or separately submitted by the Petitioner)*

The Petition references one case-control study, four cohort studies, and one case series in support of the request to reclassify ondansetron into a different pregnancy category. The Petition also references a preclinical risk evaluation that was submitted in support of the initial approval of ondansetron. The Petition expresses a specific concern about the potential for increased risk of cleft palate in neonates exposed to ondansetron in the first trimester of pregnancy, based on the findings of the single case-control study. We discuss each of these studies below.

*Case control study (1 study)*

A case-control study authored by Anderka et al.[11] and based on data from the National Birth Defects Prevention Study (NBDPS) has reported birth defects associated with exposure to ondansetron during pregnancy. The authors analyzed data on the most common non-cardiac defects (non-syndromic cleft lip with or without cleft palate, cleft palate alone, neural tube defects, and hypospadias (an anomaly of the male urethra)) from the NBDPS from 1997 to 2004. During the study period, 22,381 women participated in the NBDPS and 75 different medications and a number of herbal products were reported as treatment for NVP. In all, 4,524 cases of birth defects of interest were compared to 5,859 controls for association with NVP or its treatment in the first trimester. The authors reported that exposure to ondansetron was associated with a statistically significant 2.3-fold increase in the risk of cleft palate alone, but not of cleft lip with or without cleft palate, neural tube defects, or hypospadias.

One limitation to the case-control study by Anderka et al. is the potential for recall bias, which may arise if women who delivered infants with birth defects recall their exposure to ondansetron differently from women who delivered infants without birth defects. However, the limitation of most concern in this study is the possibility of a chance finding. According to the authors, approximately 70 comparisons between mothers with NVP who were and were not exposed to various medications were tested for statistical significance. For that number of comparisons (70), 3 to 4 comparisons are expected to achieve statistical significance by chance alone. The authors reported statistically significant associations between drug exposure and fetal anomalies for just three

[11] Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al., "Medications Used to Treat Nausea and Vomiting of Pregnancy and the Risk of Selected Birth Defects." *Birth Defects Res A Clin Mol Teratol.* 2012 Jan; 94(1):22-30. Epub 2011 Nov 19.

comparisons, including ondansetron.[12] The authors concluded that these positive associations reported in the study, which "could be chance findings," warrant further investigation.[13] Moreover, the authors noted that the medication exposure categories were not mutually exclusive (i.e., pregnant women taking ondansetron might also have been exposed to one or more other anti-NVP treatments).[14] Thus, the association of risk with certain drugs may reflect confounding by other factors for which the authors did not control, including other potentially teratogenic medication use or genetic factors.

*Cohort studies (4 studies)*

1. Pasternak et al.

Pasternak et al.[15] recently published results of a registry-based retrospective cohort study that evaluated adverse pregnancy and fetal outcomes associated with ondansetron exposure. This study relied on a historical cohort of 608,385 pregnancies from the Medical Birth Registry and the National Patient Register in Denmark between 2004 and 2011 and compared spontaneous abortion (miscarriage) (7 – 22 weeks), stillbirth (week 7 – birth), any major birth defect (first trimester), preterm delivery (< 37 weeks), and infants of low birth weight (< 2,500 grams) and small for gestational age (<10th percentile of gestational-age specific birth weights in cohort) between ondansetron-exposed and unexposed pregnancies. Of the entire cohort, 1,970 women (0.3%) received ondansetron during pregnancy (1,233 during the first trimester). These ondansetron-exposed women were matched in a ratio of 1:4 to unexposed pregnant women. The first prescription was filled at a median of 70 gestational days (approximately 10 weeks gestation) and the median number of doses per pregnancy was 30. Among ondansetron-exposed women, over half were hospitalized for NVP, including HG, and almost half received another antiemetic.

The authors concluded that ondansetron use in pregnancy did not confer an increased risk of adverse pregnancy or fetal outcomes of interest.[16] Among the 1,233 pregnancies exposed to ondansetron in the first trimester, 3% of the infants had a major birth defect

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[12] The three positive associations between drug exposure and birth defects reported in the study included exposure to ondansetron, proton pump inhibitors, and corticosteroids. See Anderka et al., supra note 11.

[13] Anderka et al., supra note 11, at 22, 29.

[14] See e.g., Anderka et al., supra note 11, at 26-27, Tables 3 and 4, note "a" (stating that medication exposure includes medications "[u]sed alone or in combination with other agents; categories are not mutually exclusive").

[15] Pasternak B, Svanstrom H, and Hviid A. "Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes." *N Engl J Med* 2013;368:814-23.

[16] The authors of this large study noted, "... we found that exposure to ondansetron in pregnancy was not associated with a significant increase in the risk of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or born small for gestational age." Id. at 823. We note that the "major birth defects" included, in addition to cleft palate and other conditions, cardiovascular malformations. Id. at Supplemental Appendix, Table S9.

compared to 3% of infants born to unexposed mothers. There were no cases of cleft palate among infants exposed to ondansetron *in utero*. The authors report 3 cases of cleft lip with or without cleft palate in the exposed cohort (0.24%) and 11 cases in the unexposed cohort (0.22%). Given the absence of cases of cleft palate alone and the small number of cleft lip (with or without cleft palate) cases, no measures of association were calculated for either defect.[17]

2. Einarson et al.

A prospective cohort study[18] from Canadian and Australian teratology information services examined the safety of ondansetron use in pregnancy among infants born to three groups of pregnant women. Each group enrolled 176 women: the first group was exposed to ondansetron, the second group to other antiemetics (Diclectin,[19] metochlopramide, phenothiazines, and ginger), and the third group consisted of women who were either exposed to no medications or only to drugs the authors considered to "be safe in pregnancy." All women in the ondansetron exposure group received medication in the first trimester of pregnancy, mostly between 5 and 9 gestational weeks.[20] No statistically significant differences were found among the three groups regarding live births, miscarriages, stillbirths, therapeutic abortions, major malformations, birth weight, or gestational age at birth.[21] We note, however, that the study was of limited size and statistical power (the study had 80% power to detect a 3.5-fold increase in major congenital malformations). Also, study enrollment was voluntary, and the comparability of ondansetron-exposed pregnant women who ultimately decided to enroll to the general population of ondansetron-exposed pregnant women is unknown.

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[17] One of the most significant limitations of any observational study is confounding (either by indication or by other data confounders and variables, such as small sample size, recall bias, possibility of a chance finding, and other data and method limitations). For this study, unmeasured or residual confounding may have impacted the overall results from Pasternak et al, but this issue was considered by the researchers with the conclusion that any magnitude change in the risk estimate would be minimal (see, e.g., discussion of modeling the effect of a hypothetical unmeasured confounder that might mask a true risk (Pasternak et al., supra note 15, at 822 and Supplementary Appendix Table 12), and discussion of post hoc analyses categorizing women according to whether they filled one prescription or two or more prescriptions for ondansetron (Id. at 818). Also, the confounding arises when comparing one cohort to another. Since there were no exposed cases of cleft palate, such a comparison could not be made.

[18] Einarson A, Maltepe C, Navioz Y, et al. "The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study." *BJOG* 2004;111:940-943.

[19] Diclectin is the pyridoxine/doxylamine drug product available in Canada. At the time of this study Diclegis (NDA 021876, held by Duchesnay), a recently-approved pyridoxine/doxylamine drug product, had not yet been approved by FDA for use in the United States.

[20] Einarson et al., supra note 18 at 941.

[21] Id. at 942.

3. Asker et al.

A retrospective cohort study by Asker et al.[22] examined pregnancy outcomes based on data obtained from the Swedish Medical Birth Register between 1995 and 2002. The study compared outcomes of women using antiemetics during pregnancy, including ondansetron, with all women giving birth during the study period. Of 665,572 pregnant women, 45 pregnant women were treated with ondansetron, with 21 women receiving ondansetron during only the first trimester, 12 during only the second to third trimesters, and another 12 throughout pregnancy (first through third trimesters). There were no reports of any major birth defects among these 45 women. This study was limited in its small sample size of pregnant women exposed to ondansetron and scant data on timing, dose, and duration of exposure to ondansetron.

In summary, the four cohort studies cited in the Petition or submitted separately by the Petitioner did not identify an increased risk of adverse pregnancy or fetal outcomes.[23] The results from the Pasternak et al. study, which is one of the largest to date on ondansetron exposure in pregnant women (1,970 women with ondansetron exposure during early pregnancy), provide some assurance regarding the fetal safety of antenatal ondansetron exposure. Specifically, the study did not identify any cases of cleft palate among the 1,233 neonates exposed to first trimester ondansetron.[24] In addition to the large size of the Pasternak study, in general, cohort studies by their design have fewer biases and confounders than case-control studies, and the cohort study by Pasternak et al. likely has fewer biases than the case-control study by Anderka et al. that supports the Petitioner's claims.

4. Danielsson et al.

A recent retrospective cohort study by Danielsson et al.[25] used data from the Swedish Medical Birth Register collected between 1998 and 2012 to assess a potential association between ondansetron use during pregnancy and a risk of congenital malformations in the infant. (An earlier analysis of this data that included births from 1995-2002 was published by Asker et al. and is briefly reviewed above (see section II.A.1.a.)). Of approximately 1.5 million births during the study period, there were 1,349 infants

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[22] Asker C, Norstedt W, Källén B. "Use of antiemetic drugs during pregnancy in Sweden." *Eur J Clin Pharmacol.* 2005 Dec; 61 (12):899-906.

[23] See section II.A.b., below, for a discussion of a cohort study by Danielsson et al., cited in a third party comment to the docket, which the authors state may indicate an association between antenatal ondansetron use and infant cardiovascular malformations.

[24] Pasternak et al., supra note 15 at 820.

[25] Danielsson B, Wikner BN, Kallen B. "Use of ondansetron during pregnancy and congenital malformations in the infant." *Reprod Toxicol* 2014 50:134-137.

exposed to ondansetron during "early pregnancy."[26] The authors report statistically significant increased associations for ondansetron exposure in early pregnancy and cardiovascular malformations and septal malformations (a type of cardiovascular malformation). The authors do not clearly describe the comparison group.[27]
Of the 1,349 infants exposed to ondansetron in early pregnancy, the only malformations occurring more than once in the study were ventricular septum malformations, ventricular and atrium septum defects, and hypospadias. The authors note that 17 of the 19 cardiovascular malformations observed in the study were ventricular and/or septal defects. In addition to noting possible confounders and other limitations, the authors note that the clinical significance of the increased reported for atrial/septal defects is unknown, and that "detailed clinical information on these cases is missing."[28] Minor atrial/septal defects are common, are often subclinical, and may resolve without intervention.[29]

Previous published studies have not reported increased associations between ondansetron use in early pregnancy and atrial and/or septal cardiovascular malformations,[30] and the signal for cardiovascular malformations reported by Danielsson et al. may or may not be causal.

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[26] The term "early pregnancy" was not defined by the authors. For purposes of our review, we assumed that "early pregnancy" was the first 12 weeks from the last menstrual period (based on information in the manuscript's Table 1). Supra note 25 at Table 1.

[27] While data from the Asker et al. study as well as the statistical methods in the current study indirectly suggest the control population consisted of the entire population of births during the study period, because the actual composition of the comparison group is not described, we had to make an assumption regarding the group for purposes of our review of the study methodology and conclusions.

[28] Supra note 25 at 137.

[29] Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39: 1890-1900.

[30] Comments submitted in support of the Petition and the September 14, 2015 supplement to the Petition included copies of or references to two abstracts of unpublished data from a cohort study, which the abstract authors state might indicate an increased risk of cardiac congenital anomalies related to antenatal ondansetron use. Both abstracts used data from the same Danish registry sources as used in the study by Pasternak et al. See Andersen JT, et al., "Ondansetron Use in Early Pregnancy and the Risk of Congenital Malformations – A Register Based Nationwide Cohort Study," International Society of Pharmaco-epidemiology, Montreal, Canada; 2013, Abstract 25, Pregnancy Session 1 and Andersen JT, et al., "Ondansetron Use In Early Pregnancy And The Risk Of Congenital Malformations –A Register Based Nationwide Cohort Study," http://www.acog.org/~/media/Districts/District%20II/PDFs/Ondansetron_Use_031514_eNewsletter.pdf . FDA staff reviewed and considered these abstracts, but determined there was insufficient information to meaningfully interpret the abstract results. As of October 9, 2015, the Petitioner and commenters have not provided, and FDA has not found in the literature, reviewable published study data regarding these abstracts.

*Retrospective case series (1 case series)*

In a retrospective case series covering 2002 to 2011, Ferreira et al.[31] described outcomes in 14 pregnant women who were treated with ondansetron for HG. No fetal anomalies attributable to ondansetron use were reported.[32]

*Preclinical safety evaluation*

In 1989, Tucker et al. published the results of a preclinical safety evaluation of ondansetron.[33] This evaluation was submitted in support of the 1991 approval of Zofran, and certain information from it is included in labeling for Zofran drug products.[34]

The reproduction studies conducted as part of the safety evaluation are relevant to this Petition. Tucker et al. described results from reproduction studies performed in pregnant rats and rabbits given ondansetron IV doses up to 4 mg/kg per day, which is approximately 1.5 to 3 times the recommended human IV dose of 0.15 mg/kg given three times daily. These studies did not show any evidence of impaired fertility or harm to the fetus due to ondansetron. Ondansetron was classified as pregnancy category B based on these negative findings (but was appropriately not classified as pregnancy category A[35] because of a lack of adequate and well-controlled studies in pregnant women confirming these findings during human use of the drug product).

*b. Additional Information Reviewed by FDA*

In addition to reviewing the studies cited in the Petition,[36] supplements, and third-party submissions to the docket,[37] we also performed an independent search of the published medical and scientific literature. This search did not yield any additional human studies about ondansetron exposure and adverse pregnancy, fetal, or neonatal outcomes.

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[31] Ferreira E, Gillet M, Lelievre J, Bussieres JF. "Ondansetron use during pregnancy: a case series." *J Popul Ther Clin Pharmacol.* 2012; 19(1); e1-e10.

[32] Id. at e8.

[33] Tucker ML, Jackson MR, Scales MD, Spurling NW, Tweats DJ, Capel-Edwards K. "Ondansetron: pre-clinical safety evaluation." *Eur J Cancer Clin Oncol.* 1989; Suppl 1: S79-93.

[34] See, e.g., labeling approved for Zofran injection on September 18, 2014, at Section 8.1 (Pregnancy), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf .

[35] The regulations in effect when the Petition was submitted in 2013 specified the following criteria for a pregnancy risk Category A designation: "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(1) and 201.80(f)(6)(i)(a)).

[36] While all studies cited in the Petition were reviewed, this response does not include separate discussion of each study. All were considered by FDA and included as part of the totality of the evidence reviewed in connection with the Petition, but not all were considered integral to the discussion in this response.

[37] These include 13 submissions, which are listed in note 2, above. The submissions may be viewed online at www.regulations.gov (Docket No. FDA-2013-P-0048).

*c. Analysis and Conclusions*

In summary, of all the studies, case reports, and other data we reviewed, only two studies (the case-control study by Anderka et al. discussed on pp. 7-8, above, and the retrospective cohort study by Danielsson et al. discussed on pp. 10-11, above) provided information that suggests adverse outcomes for the pregnant woman, fetus, or neonate.[38]

The Anderka et al. study has methodological limitations; its finding of a modest positive association between cleft palate and ondansetron exposure may be a chance finding; and the association has not been observed in other published studies.[39] The Danielsson et al. study also has methodological limitations, a modest positive association between cardiovascular malformations and ondansetron that may be due to non-causal factors, and an association not observed in other published studies.[40] Indeed, a recent observational cohort study from Denmark (Pasternak et al.), a large study on the safety of ondansetron in pregnancy, contradicts the findings in the Anderka et al. study with regard to an association between ondansetron use during pregnancy and cleft palate, as well as finding no association between ondansetron use and a panel of "major birth defects" including, but not limited to, cardiovascular malformations.[41] While the Pasternak et al. study also has some methodological limitations, the authors did not detect any increased risk to the fetus. Furthermore, the study did not identify a single ondansetron-exposed cleft palate case, suggesting a lack of association.

All these studies suffer from various methodological limitations[42] that preclude definitive conclusions about the safety of ondansetron use in pregnancy. The available evidence is not sufficient to conclude that there is an increased risk of birth defects, including cleft palate, among fetuses exposed to ondansetron. Moreover, the additional information we reviewed (e.g., results of an independent literature search and adverse event reports) does not provide evidence of a safety concern related to the use of ondansetron during pregnancy. When reviewed together, the totality of the available data does not support a determination that there is an increased risk of fetal adverse outcomes, including cleft palate, among fetuses exposed to ondansetron, because none of the other published studies corroborate the findings in the Anderka et al. or Danielsson, et al. studies. While a potential association between ondansetron use during pregnancy and cardiovascular malformations warrants continued vigilance, given the limitations of the Danielsson study, as well as the lack of consistent evidence for cardiovascular teratogenicity, the study does not support a change in pregnancy risk category at this time for those products

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[38] Please also see note 30, above (discussing abstracts of unpublished data from a cohort study that the abstract authors state might indicate a risk of congenital anomalies related to antenatal ondansetron use).

[39] See discussion of the Anderka study on pp. 7-8, above.

[40] See discussion of the Danielsson study on pp. 10-11, above; see also note 30, above.

[41] Supra note 15.

[42] For example, small sample size, data confounders, recall bias, possibility of a chance finding, and other data and method limitations.

for which the labeling has not yet been revised consistent with the Pregnancy and Lactation Labeling Rule. For products for which the labeling is currently undergoing revision to be consistent with the new rule, the data reviewed do not provide sufficient evidence to support changes to the "Pregnancy" and "Lactation" (formerly "Nursing Mothers") label subsections at this time.

Thus, we find that the available data are not sufficient to conclude that there is a safety concern with regard to the use of ondansetron during pregnancy that would warrant changes at this time to the pregnancy risk category (for labeling that has not yet been revised consistent with the Pregnancy and Lactation Labeling Rule), or to the "Pregnancy" or "Lactation" subsections in labeling that is being revised consistent with the new rule.

*2. Risks to the Pregnant Patient*

In addition to concerns regarding potential teratogenic risks to the fetus and neonate posed by ondansetron use during pregnancy, the Petition also raises concerns regarding risks specific to the pregnant woman.

*a. Vision Loss*

The first supplement to the Petition is a case report of one pregnant woman who experienced vision loss while being treated with ondansetron.[43] We reviewed the case report as well as other literature and adverse event reports from the FDA Adverse Event Reporting System (FAERS) database, in order to identify cases of vision loss related to ondansetron. FAERS is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products.[44] FDA requires sponsors of prescription products, including sponsors of ondansetron products, to report adverse events associated with their drug products.[45] In addition, individual health care providers and their patients are encouraged to voluntarily report serious adverse events to FDA.[46] Transient blindness and blurred vision are labeled as potential adverse reactions for any patient using ondansetron

[43] Davis, F, et al., "The Case Files: Vision Loss in a Pregnant Patient," *Emergency Med News*; 2012.

[44] See FDA Adverse Event Reporting System (FAERS), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm .

[45] See, e.g., 21 CFR part 314.80(c)(1)(i) (among other things, requiring reports to FDA within 15 calendar days when sponsors of prescription products become aware of information that suggests that use of the drug product resulted in an adverse drug experience that is both serious and unexpected ).

[46] See, e.g., MedWatch forms and other information regarding voluntary reporting by health professionals and consumers available at the FDA website (http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm ).

products.[47] We did not find evidence to support a potential safety signal for vision loss in pregnant women treated with ondansetron (as opposed to any patient treated with ondansetron).

*b. Torsade de Pointes, QT Prolongation, and Use of Ondansetron with an Infusion Pump*

The Petition raises a number of concerns regarding certain potential adverse reactions to ondansetron and the use of ondansetron with an infusion pump for treatment of NVP. In particular:

- The Petition states that Torsade de Pointes and QT prolongation are of particular concern when ondansetron is used in pregnant women (Petition at 4) and notes that women with NVP may already have electrolyte imbalances.

- The Petition states that use of a subcutaneous pump to administer ondansetron to pregnant women is particularly worrisome, citing a 2012 safety warning from FDA regarding the 32 mg IV dose of ondansetron[48] to support this concern and further states that it is "not uncommon" for patients to receive ondansetron doses approaching or exceeding 32 mg per day (Petition at 4).

- The Petition states that few obstetricians are aware of the FDA precautions and, therefore, are not following the safety recommendations (Petition at 4).

We discuss each of these issues below.

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[47] See, e.g., labeling approved for Zofran injection on September 18, 2014, at Section 6.2 (Postmarket Experience), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf .

[48] Drug Safety Communication: New information regarding QT prolongation with ondansetron (Zofran) (June 29, 2012), http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm. The NDA sponsor announced immediate changes to the drug labeling to remove the 32 mg single IV dose. Id. Throughout 2012 and early 2013, FDA worked with brand name and generic drug sponsors on a voluntary recall of the 32 mg IV ondansetron product. See Drug Safety Communication: Updated information on 32 mg intravenous ondansetron (Zofran) dose and pre-mixed ondansetron products (December 4, 2012), http://www.fda.gov/Drugs/DrugSafety/ucm330049.htm. More recently, FDA published a determination that the 32 mg single IV dose was withdrawn for reasons of safety or effectiveness, see *Federal Register* Notice, "Determination That Ondansetron (Ondansetron Hydrochloride) Injection, USP in PL 2408 Plastic Container, 32 Milligrams in 50 Milliliters, Was Withdrawn From Sale for Reasons of Safety or Effectiveness" (80 FR 32962, June 10, 2015), and a related notice that FDA has withdrawn approval of the NDA (and four ANDAs) for that ondansetron product, see *Federal Register* Notice, "Baxter Healthcare Corporation et al.; Withdrawal of Approval of One New Drug Application and Four Abbreviated New Drug Applications (80 FR 32966, June 10, 2015).

*Current Labeling Regarding Torsade de Points, QT Prolongation, and Electrolytes*

Both Torsade de Pointes and QT prolongation are already clearly identified on current ondansetron labeling as potential adverse reactions for health care providers to consider before treating any patient with ondansetron, whether pregnant or not.[49] The labeled information also includes a specific warning regarding additional monitoring recommended for patients with electrolyte imbalances.[50] OB/GYNs caring for pregnant women have access to, and should understand, this labeling. Moreover, OB/GYNs caring for women with NVP are likely to be especially aware of electrolyte balance concerns.

*Use of an Infusion Pump to Administer Ondansetron for NVP*

Ondansetron has not been approved to treat NVP (as noted in the Background section above) and no infusion pump has been cleared or approved for use in delivering ondansetron subcutaneously for treatment of NVP. Thus, such delivery of ondansetron to treat NVP would be an unapproved use of both ondansetron and the infusion pump used to deliver it.

FDA's 2012 safety communication regarding ondansetron communicated preliminary study results that suggested that a 32 mg single dose of intravenous ondansetron may affect the electrical activity of the heart by causing QT prolongation, which could predispose patients to develop Torsade de Pointes. In response, Zofran's sponsor (GlaxoSmithKline) voluntarily removed the 32 mg single intravenous dose of Zofran from the market. The FDA safety communication also noted that it did not apply to the oral dosing regimens or to the other lower intravenous dosing regimens.[51] We also note that the FDA safety communication was related to the peak blood concentration after administering 32 mg in a single intravenous dose, not to 32 mg total ondansetron per day, which appears to be the concern raised in the Petition. In addition, under current labeling, the maximum amount of ondansetron (Zofran) that may be given per dose is 16 mg (every 4 hours for a total of three doses in adults with chemotherapy-induced nausea and vomiting), to be administered intravenously over 15 minutes. As noted above, there are specific labeled warnings regarding Torsade de Points, QT prolongation, and electrolyte imbalances.[52]

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[49] See, e.g., labeling approved for Zofran injection on September 18, 2014, at "Warnings and Precautions," and Sections 5.2 (QT Prolongation), 17 (Patient Counseling Information), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf.

[50] Id. at Section 5.2 (QT Prolongation) ("... ECG [electrocardiogram] monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation).

[51] See note 49, above, Drug Safety Communication: New information regarding QT prolongation with ondansetron (Zofran) (stating, "[t]he new information on QT prolongation does not change any of the recommended oral dosing regimens for ondansetron. It also does not change the recommended lower dose intravenous dosing of ondansetron to prevent post-operative nausea and vomiting.").

[52] See notes 48, 50, and 51, above.

The Petition states that it is "not uncommon" for infusion pump patients to receive ondansetron doses approaching or even exceeding 32 mg per day (Petition at 4). However, the Petition does not include sufficient data to support this statement and we are not independently aware of such data.[53]

In summary, our review of your Petition did not find evidence to support your concerns regarding treatment of pregnant women with a total dose of 32 mg of ondansetron over a 24 hour period via infusion pump.

*OB/GYN Awareness of FDA Precautions Regarding Ondansetron Use*

The Petition states that few obstetricians are aware of FDA's cautions regarding the use of ondansetron (Petition at 4). However, we did not receive or find in our own research sufficient data to support this statement. To the contrary, given the clear risk labeling with regard to QT prolongation, Torsade de Pointes, and electrolyte imbalances, as well as the existence of professional obstetrical advisories such as the *ACOG Practice Bulletin* on treatment of NVP,[54] we believe that OB/GYNs already have a significant amount of information available regarding these risks. Reviewing and applying such information to treat an individual patient is a routine part of a physician's practice of medicine.

Although the Petition does not address post-marketing safety surveillance, we note that in addition to the drug product post-marketing surveillance discussed above (see section 2.A.2.a), FDA requires device manufacturers and device user facilities to report to us if they become aware of information that reasonably suggests that use of their infusion pump may have caused or contributed to a serious injury or death.[55] In addition, individual health care providers and their patients are encouraged to voluntarily notify the manufacturer or sponsor when they become aware of such events and to make reports to FDA. Such mandatory and voluntary reports provide an ongoing method to alert FDA to situations where an adverse outcome may have been caused by the use of an infusion pump to deliver ondansetron. As part of our consideration of this Petition, we reviewed relevant adverse event post-marketing surveillance data for ondansetron and for infusion pumps. As of May 1, 2015, we did not find any reports of adverse outcomes related to ondansetron administration to pregnant women via infusion pump.

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[53] The Petition does not cite any specific source to support the statement that it is "not uncommon" for infusion pump patients to receive ondansetron doses approaching or even exceeding 32 mg per day. FDA reviewed the dosage instructions in the labeling, current practice guidelines for OB/GYNs, adverse event reporting for both drugs and devices, and other information. The reviewed data did not support the petition's statement that patients commonly receive doses exceeding 32 mg per day.

[54] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, "Nausea and Vomiting of Pregnancy," Number 153, September 2015.

[55] See, e.g., 21 CFR part 803 Subpart E. In addition, device user facilities, including outpatient treatment facilities and hospitals, are required to submit reports to both FDA and the manufacturer of the device, if known, when they become aware that a device has or may have caused or contributed to the death of a patient in their facility (section 519(b) of the Act and 21 CFR part 803 Subpart C).

## B. Petition Requests

### *1. Request to Reclassify the Drug Ondansetron from Pregnancy Risk Category B to Category C, D, or X after Evaluation of "New Safety Information"*

The Petition requests that FDA reclassify ondansetron from pregnancy risk category B to category C, D, or X after consideration of new safety information (Petition at 1). We have considered this request, and for the reasons discussed below, we have determined that the Petition has not provided sufficient information to justify changing the pregnancy category. Additionally, as noted, the recently published Pregnancy and Lactation Labeling Rule requires the removal of the pregnancy categories from prescription drug and biological product labeling.

We also note that, based on the available data reviewed in connection with this Petition[56] and the issues raised in the Petition, you have not provided sufficient evidence to support changes at this time to the new "Pregnancy" and "Lactation" (formerly "Nursing Mothers") labeling subsections for ondansetron that are undergoing PLLR conversion. Safety evidence for ondansetron use during pregnancy consists of two large observational studies, supplemented by small non-interventional studies and case reports. In contrast, other than a single case-control study (Anderka et al.) and one recent retrospective cohort study (Danielsson et al.), none of the other published and reviewable sources cited in the Petition, supplements, and comments, or found in our own literature search, review of adverse event reports, and other data, found evidence of adverse pregnancy, fetal, or neonatal outcomes related to ondansetron use.

Taking into consideration both the data available at the time ondansetron was approved and subsequent human data gathered in the post approval setting, at this time the totality of the data do not support a conclusion that there is an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac ventricular and/or septal defects, among fetuses exposed to ondansetron. Because the new Pregnancy and Lactation Labeling Rule eliminates future use of the pregnancy risk categories, we have not discussed each category in detail. As discussed above, we believe pregnancy category B was the appropriate risk category for ondansetron when it was assigned and, to the extent that the pregnancy categories remain in the labeling for any ondansetron products until the Pregnancy and Lactation Labeling Rule is fully implemented, we believe pregnancy category B remains appropriate today.

As the labeling for ondansetron products is updated to comply with the new content and format requirements of the Pregnancy and Lactation Labeling Rule, it will include

[56] When discussing "available data" reviewed by FDA in connection with this Petition, we mean all materials submitted to the docket by the Petitioner, all third-party submissions to the docket, and additional information reviewed by FDA, including, but not limited to, post-marketing drug and device adverse event data, information submitted by the sponsor to support approval of the ondansetron NDA, and targeted searches of the published literature.

appropriate data to describe the known risks if taken during pregnancy.

Accordingly, this request is denied.

2. *Request to Notify OB/GYNs there is Insufficient Scientifically Acceptable Evidence that Ondansetron is Associated with Improved Treatment Outcomes and May Lead to Adverse Maternal and Fetal Events or Outcomes*

The Petition requests that FDA notify OB/GYNs that: (a) insufficient scientifically acceptable evidence has been published demonstrating safety, efficacy, or superiority of ondansetron over conventional treatments for NVP and (b) its use may lead to adverse maternal or fetal outcomes (Petition at 2).

*a. Notification Regarding Safety*

As discussed above in sections II.A.1.c, II.A.2.a-b, and II.B.1, we do not agree with the Petition that the available data reviewed by FDA in connection with the Petition warrant a conclusion that ondansetron use during pregnancy poses an increased risk of fetal or maternal adverse outcomes. Thus, a notification to OB/GYNs that ondansetron may lead to adverse maternal or fetal outcomes is not necessary and could be misleading. In particular, the available data do not support a conclusion that there are increased safety risks for the expectant mother, such as vision loss or QT prolongation (beyond the risks faced by any patient using ondansetron) (see section A.2), or for the fetus or neonate, including cleft palate (see section A.1).

*b. Notification Regarding Efficacy*

As noted, ondansetron is not approved for treatment of NVP, nor is there information in the labeling regarding ondansetron's efficacy as an NVP treatment or its relative efficacy as compared with other NVP treatments.

You have not provided a basis for us to notify OB/GYNs that there are insufficient data on the efficacy of ondansetron for treatment of NVP, or on its relative superiority or inferiority as compared with other NVP treatments. In particular, the Petition states that there are only a small number of studies regarding the efficacy of ondansetron in treating NVP or its relative efficacy for that use as compared with other NVP treatments (Petition at 2-3). While this may be true, ondansetron is not approved for use to treat NVP. Absent a compelling legal or public health concern, FDA generally does not comment on the number or quality of studies regarding the efficacy of a drug product for an unapproved use or provide notification to health care providers regarding its relative efficacy as compared to other drug products for such unapproved use. FDA does not believe that such an unusual notification is warranted in this case.

In summary, we believe the data we reviewed do not warrant a special notification to OB/GYNs regarding safety concerns related to the use of ondansetron in the treatment of NVP or a notification regarding insufficient efficacy data regarding such use.

Accordingly, this request is denied.

3. *Request to Notify OB/GYNs that Promotion of Continuous Subcutaneous Ondansetron Pump for the Treatment of Nausea and Vomiting of Pregnancy is a Violation of FDA Regulations*

The Petition requests that FDA notify OB/GYNs that the "continuous subcutaneous ondansetron pump" may not be marketed or promoted in any way in the absence of FDA approval for the indication of treatment of NVP and that such promotion is a violation of FDA regulations (Petition at 1).

As stated in section A.2.b., above, based on the available data submitted to FDA in support of the Petition and information researched independently by FDA (e.g., adverse event data), FDA does not have reason to believe that the treatment of pregnant women with ondansetron via infusion pump is a safety concern warranting FDA action.

For this reason, we deny this request.

## III. CONCLUSION

Based on our review of the Petition, supplements, additional submissions to the docket, and the scientific literature, as well as our review of other pertinent data and information, including published literature not referenced in the Petition, supplements, or docket, and adverse event reporting information, we deny the requests in the Petition for the reasons discussed above.

Although we have denied your requested actions, we nevertheless appreciate the information you provided. We will continue to monitor information regarding the use of ondansetron during pregnancy. As with all drug products, we will continue to engage in postmarketing surveillance and review other safety data regarding ondansetron and take any actions as appropriate.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research